

TB Alliance World TB Day Press Call
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Gwynne Oosterbaan: Good morning and good afternoon to those of you joining us from Europe.

This is Gwynne Oosterbaan. I'm in charge of Communications at the Global Alliance for TB Drug Development.

This is our 2005 World TB Day Press Call. And we're very pleased that you're able to join us.

I'd like to introduce Dr. Maria Freire who's the President and CEO of the TB Alliance. Maria?

Maria Freire: Good morning and afternoon to those of you from all over the world. We really are delighted that you're joining us today.

World TB Day for us is a milestone every year which allows us to take stock of what has happened in the prior year. And this year in particular, we're delighted to be able to celebrate World TB Day with the announcement of the agreement between the TB Alliance and GSK.

I think it's important for us to put the pipeline and the idea of new drugs into perspective. I'm sure that many of you on the call already know, but it's important to remind ourselves, that there are about 8 million new cases of tuberculosis in the world every year with about two million deaths, which represents an enormous public health problem.

We have a regimen that, of course, does work, and it's important for us to remember this, but it is a long and cumbersome regimen. This is why we are excited to talk to you today about the status of the TB drug pipeline. We believe that we have -- for the first time in over 40 years -- the possibility of a completely new and revolutionary regimen, a regimen that will take two months or three months to complete. This is a tremendous "quantum leap" for the field and certainly for TB control.

We hope that when we finish the call today, you will get this sense of excitement around the global pipeline; that you will better understand where this important agreement between GSK and the Alliance sits within that pipeline; and also, appreciate the important commitment of all the people who are working in this field today, and understand the Alliance's commitment to them. We have what we like to call our "Triple A" mandate which ensures the

affordability, the adoption, and the access of this new regimen for all people around the world who need it.

We have a group of speakers today that represent both the Alliance and GSK, and importantly, a representative from CDC and a representative from Treatment Action Group or TAG.

I will introduce them each individually and at the end of their presentations we will take Q&A.

So the first speaker will be Dr. Dr. Mel Spigelman who is Director for R&D for the TB Alliance.

The second speaker is Dr. David Pompliano, Vice President and Head of Biology, at GlaxoSmithKline.

And the following speaker would be Dr. Ken Castro, who is Assistant Surgeon General and Chief of the Tuberculosis Elimination Branch Division at the Centers for Disease Control and Prevention (CDC).

And last but certainly not least, we have Mark Harrington, who is Executive Director of the Treatment Action Group or TAG.

With no further ado, I hand the microphone to Dr. Spigelman.

Mel Spigelman: Maria, thank you very much.

This is Mel Spigelman from the TB Alliance.

What I'd like to do in the next few minutes is really put into context this new agreement with GSK and the TB Alliance and show why we're extremely optimistic that this will add tremendous importance and strength to the global pipeline for new TB drugs.

I think, as Maria may have alluded to, if we look back just a few years ago, there really was no TB pipeline and there really was not that much hope of having new drugs on the horizon within almost any timeframe that would be of real importance. And that really has changed dramatically -- even over the last two to three years.

And what I'd like to do is outline that pipeline a little bit and then go into the true significance as we see it for this relationship with GSK.

We now stand on the exciting almost precipice of having six or seven new drugs that could enter clinical trials this year which really is a truly revolutionary finding for - revolutionary development for the field of TB.

I think as anybody knows who has done drug development, however, one needs to have a pipeline that continually feeds new drugs into the clinic, because of the risks that are inherent in doing any sort of new drug research and development.

And that brings us really to the TB Alliance's relationship with Glaxo.

Glaxo -- and I'll say this because David Pompliano who'll speak next may be too bashful to tout his own horn -- Glaxo, as you all know, is the second largest pharmaceutical company in the world. They have one of the largest antimicrobial programs in the world, having made a major commitment to the field of antimicrobial research. And because of those assets and that commitment, they bring fantastic resources to bear in research and discovery for TB.

So clearly being able to leverage the resources of an organization like GSK is of tremendous importance.

And we think that the combination of having the TB Alliance with the TB-specific knowledge that we bring -- based on the variety of partnerships and associations we have with virtually all the players who work in the field of TB around the world today, with the GSK program backed by their financial resources, we will help to solve this problem. This is a tremendously synergistic program between ourselves and Glaxo, with ample capacity for pushing these projects forward.

With the projects that we've outlined, and David will go into more detail, we will basically double the TB Alliance's discovery program .

So with that, let me turn it over to Dr. David Pompliano from GSK who will have responsibility for this program from the GSK perspective. And I think David will be going into much more detail on the actual projects that we'll be working on together.

David?

David Pompliano: Yes, indeed. Thank you, Mel. I do very much appreciate it.

I am David Pompliano from GSK. And on behalf of GSK, I really just want to say how excited and very proud we are to be collaborating with the TB

Alliance to help find new and better therapies for the treatment of tuberculosis.

So I guess first I should tell you what GSK brings to the table for this collaboration.

First, we have established a research facility in Tres Cantos, Spain, which is just outside of Madrid, that's really fully staffed with seasoned drug hunters dedicated to the discovery of new drugs for both TB and malaria. Collaboration with the TB Alliance will allow us to add significantly to the capability of this research site. And of course that will greatly help accelerate the early stage compounds into the clinic.

Now another important thing about this group is that they're not operating in isolation. They are plugged into the larger GSK discovery organization. And as such, they have access to all the resources and expertise, high throughput screening, bioinformatics, protein expression, research management experience and clinical experience that all the other therapy areas have. And of course, we hold that site to the same standard we would hold any other therapeutic area.

Okay, so with that as sort of a little bit of an introduction of what we're doing, I just want to go over the portfolio a little bit -- portfolio starting with four programs, two of which capitalize on existing antibacterial programs within GSK since we do have, as Mel mentioned, quite an active antibacterial program; and the other two of which are just the beginning of the discovery process and they're much more TB-specific. In the earliest stage projects we're looking for new lead compounds by running high throughput screenings of GSK's chemical libraries against the molecular TB target.

Okay, so the first advanced program, really the most advanced program, is the pleuromutilin program. And the pleuromutilin program is a class of compound already known to be antibacterial. It's been underway for some time at GSK.

The goal in this program is to now have chemists modify the core pleuromutilin structure to optimize the antibacterial activity against TB, and to also incorporate into those molecules appropriate drug-like properties that would allow us to administer them safely into humans.

Now these pleuromutilins act by blocking protein synthesis. And in this regard, they really do share the same general mechanism as many very potent antibacterials that are already out there -- macrolides, tetracycline oxazolidinone, for example.

But the important thing here is they have different chemical structures and they bind into the ribosome in a unique way and that are unlike any existing class of antibiotic.

And we also found in the laboratory that resistance is very slow to develop. And that is that no single mutation in the ribosome will lead to a high level of resistance.

We've already made something close to over 500 analogs in this class and we're in a much better position now to understand the properties that endow the molecule with anti-TB activity.

So that's a very promising-looking program.

The second program is really sort of an earlier version of the pleuromutilin program. And this - as I mentioned GSK has been active in antibacterial and antimicrobials in general over the years, and so we have a number of compounds in our library that target very specific molecular entities within bacterial or other microbes.

For example, the ones we're going to be looking at most closely in the context of the collaboration with the TB Alliance is DNA gyrase inhibitors which are the target of quinolones for example. And quinolones are the target -- actually attacked not target -- peptide deformylase, another protein synthesis target, and also electron transport inhibitors.

And so what we're doing now is we're going back to all those compounds which we know - molecular targets - and looking for anti-TB activity. And of course if we find groups of compounds that actually have anti-TB activity and look very developable, our chemistry teams would be put on those and we can then develop them specifically for TB.

The last two programs we have are at the screening stages, as I've mentioned already. One of them is a protein called InhA which is really an enzyme involving fatty acid biosynthesis. It's an enoyl ACP reductase. It's an essential target. And if you knock that target out in TB, the bacteria die. They die very rapidly.

It's also the target of isoniazid, one of the key drugs and a normal regimen for TB.

The problem with isoniazid is that - really the pro-drug and needs to be activated by an enzyme in TB called catalase before it can block the InhA protein. So our idea here is to directly try to inhibit the InhA molecule and to

try to avoid that activation step. That should avoid a lot of the resistances that have already developed against isoniazid.

The last project is isocitrate lyase. This is an enzyme that's required for survival during the persistent phase of TB. That is when the bacterium is - as if were hiding out in macrophage in the body.

This is a very difficult form of TB to treat. And so, we would love to have a new therapy for this. This would have the great potential to dramatically shorten the treatment time for TB.

So during this latent phase, the metabolism in TB bacterium actually changes from - if they were eating glucose to sort of eating fatty acids. And isocitrate lyase is an enzyme that's absolutely required to survive on the products or the breakdown products of fatty acid.

Studies in animals have already shown that the TB bacterium cannot maintain the persistent infection without the presence of this protein. So I think this is a very exciting new type of target and could really mean a breakthrough for TB therapy, at least in the persistent phase.

So this is pretty much the portfolio we will begin with and may expand as we identify other targets – and the program is designed give us the flexibility to jump on new exciting targets.

And I guess that pretty much completes my overview. I would now like to hand over to Ken Castro from the CDC.

Kenneth Castro: Thank you very much. This is Ken Castro.

Let me add that we share in the excitement of the recent advances to improve the pipeline for new tuberculosis drugs.

From the perspective of the Department of Health and Human Services and the Centers for Disease Control and Prevention, I'd like to share three points.

First is there is an urgent need for evaluating new drugs in tuberculosis clinical trials. The length of treatment now required to achieve a cure and the occurrence of multi-drug resistant tuberculosis threatens very hard-earned gains in global TB control. So we're going to need these new tools.

Secondly, CDC is committed to maintaining its long-term support for the Tuberculosis Trials Consortium which is an infrastructure for multi-center clinical trials and brings together academicians with public health departments in the United States, Canada, Brazil, Spain, South Africa, and Uganda.

The nature of these clinical trials requires a stable infrastructure with the latest, clinical, laboratory, and statistical research capacity. They imply a long-term commitment.

The benefits in improving patient care are readily apparent in the latest recommendations for the treatment of tuberculosis, but we must do better.

And third, public and private partnerships such as you're seeing between the Department of Health and Human Services, CDC, National Institutes of Health and the Global Alliance and GlaxoSmithKline are key to ensuring the desired synergies and ensure that the very needed trials take place and advance into routine practice.

At the end of the day, we need to be able to ensure that people with tuberculosis have access to care, get cured, and are not overly cumbersome in order to achieve the desired cure.

With that, I end my remarks and I think very appropriately turn it over to Mark Harrington. I'm very happy to have Mark from the Treatment Action Group and a well-recognized AIDS activist involved in this effort which has been in my opinion lacking in tuberculosis up until very recently.

Mark, the floor is yours.

Mark Harrington: Well, thanks, Ken.

And I want to thank the organizers from the Global Alliance for TB Drug Development for asking me to be on this call. I think it is a good opportunity to highlight the need for communities of people affected by HIV-AIDS to be more involved in the fight against TB.

And it also shows I think that some lessons can be learned in TB drug development -- that we can speed up drug development and licensing and access and approval, and then more broadly distribute new drugs around the world that has always been the case in the past.

I just wanted to make a few case points about the problem of TB among people with HIV.

First of all, the global strategy for controlling TB which is called DOTS is really only directed against TB cases that are smear-positive. And two thirds of HIV-infected TB cases are not smear-positive and so they wouldn't necessarily be caught by the DOTS program. And in many parts of the world

such as in Sub-Saharan Africa, less than 30% of people living with HIV-AIDS even have access to a functioning DOTS program.

So there's a big problem with access even to existing regimens. And then there's the problem that the existing regimens take so long, takes from 6 to 8 months for a first-line therapy and can take as long as 18 months for multi-drug resistant TB. And so powerful new compounds and shorter regimens are desperately needed.

There were almost 1 million new cases of tuberculosis amongst people living with HIV in 2003. There were about 300,000 deaths caused by TB in people living with HIV-AIDS the last year for which data are available.

So TB affects a third of people with AIDS and it causes death in at least a tenth of people with AIDS.

Another big problem is that the most common first-line drug used to treat HIV, the non-nucleoside (nevirapin) and protease inhibitors, those drugs are difficult or impossible to use with the most common first-line TB drug regimens which contain rifampin.

So we desperately need new drugs for TB that can be used in conjunction with the first-line antiretroviral regimen and vice versa.

And therefore, the early commencement of drug interaction studies between new TB drugs and widely-used antiretrovirals will be a central step in TB drug development and one that we will be advocating with the Global Alliance for TB Drug Development and its partners in industry to make sure that those steps are taken.

And I think more broadly, the involvement of communities of people living with or affected by TB and HIV should be a central part of the drug development process and can indeed be a very helpful part in speeding access and making studies more relevant to communities and in ultimately getting the new drug to the people who need them.

Thank you very much.

Maria Freire: Thank you, Mark, this is Maria Freire. And certainly your comments and those of David and Ken and Mel are very well put.

We clearly need to develop the new medicines with the expectation that a large percentage of the patients taking these drugs will be HIV positive. And so every drug that we develop at the TB alliance, every drug that's part of our

portfolio is tested for interactions with ARV's to ensure that there is a synergy between the two regimens.

So, I guess, the concluding remarks that I have is that we have come a long way as Mel indicated and David reinforced and I think that the excitement that you're feeling from the CDC and Ken's comments on the importance of having these new regimens tested really bring together a new sense of excitement in the field.

We are celebrating this year's World TB Day with excitement, albeit cautious excitement, as anybody that develops new medicine understands and appreciates that there's attrition and there are drugs that eventually will not make it.

However, the fact that we have a global portfolio, the fact that we have these different molecules that are going to hopefully be in clinical testing in a very short period of time gives us reason for optimism and reason to believe that not only will we have a shorter treatment but we will have hopefully have a new revolutionary regimen that will be made accessible to all people who need it.

I will hand the microphone over to Gwynne Oosterbaan from the TB Alliance and ask her to monitor the questions from anybody who would be interested in going into a bit more of the specifics.

Thank you.

Gwynne?

Gwynne Oosterbaan: All right.

Operator, we're ready to take any questions that have come up already.

I just want to thank everyone again for their prepared remarks.

Conference Coordinator: Okay.

And at this time, if you would like to ask a question, please press the star and 1 on your touchtone phone. You may withdraw your question at any time by pressing the pound key.

Once again, to ask a question, please press the star and 1 on your touchtone phone.

We'll take our first question from Donald McNeil with the New York Times. Go ahead please.

Donald McNeil: Hi.

The question I have is "Will those paying for the research methods pay for the clinical trials when those start?"

Gwynne Oosterbaan: I think we'll have Dr. Mel Spigelman answer that question from the TB Alliance.

(Mel Steve): I'm sorry, Donald, when the...

Donald McNeil: Who's paying for both the research, on the drugs themselves, (unintelligible) and then paying for the clinical trials when those start?

Mel Spigelman: Oh, the research costs are basically split between the TB Alliance and GSK. We are both contributing to those.

The site at Tres Cantos which is the research site dedicated to TB and malaria within GSK will be hiring 25 new scientists in addition to the staff that's already there to dedicate to the work on TB. And we will be sharing in the added cost with GSK.

Regarding the clinical trials, we will basically decide that when we get to that point so that there is no preset agreement at this point on how we will be doing that.

Clearly, from the work that we've done in the past, and what's ongoing now, this is where organizations like Ken Castro's become extremely important and that the TBTC consortium that Ken alluded to, we already are working with them on other clinical trials, and we would certainly expect to do that not only for the foreseeable future but even further on down the line.

Donald McNeil: Is there money - any money budgeted for this or any money put aside? Clinical trials are expensive, so the question is...

Mel Spigelman: Yes.

Donald McNeil: ...if you do develop - if one of these four projects works out, that there's going to be millions of dollars need to be found to see if it works in humans. What have - what - been doing that right now?

Mel Spigelman: Yes, we certainly plan to participate in the funding for any clinical trials that will evolve from this research as well as from the global research that's going on in a variety of other projects.

And, Donald, you're completely right, if anything, the majority of money that needs to be spent in R&D is consumed in the clinical phase rather than in the research phase. We certainly are aware of that and part of our planning is to make sure that that funding will be available.

Maria Freire: Donald, this is Maria Freire from the TB Alliance.

We have a very active relationship with our funders. We have forecast not only these costs but other costs in our pipeline. It is our expectation that we will share the cost with GlaxoSmithKline. But we have done the mathematics, we do know the expectations for the cost of these trials, and we are generously supported by the Bill & Melinda Gates Foundation, the Rockefeller Foundation, the US Government through USAID, and the Dutch Government.

Of course, as Mel said, these trials are expensive and we need to continue to ensure that the funding is made available. But for every drug that we bring into our pipeline and our portfolio, particularly when it gets into the clinical trials, we have to ensure that we have the money to carry the clinical trials further.

In the case of the GSK agreement, this is an early discovery agreement. We do not have any lead right now that we expect will be going into the clinic in short order, but there are other compounds in our portfolio where that is the case.

So, indeed, we're very sure and cognizant of that fact and we do budget accordingly and establish our projections precisely this way.

Ken Castro: This is Ken Castro.

Let me also add that from the Federal Government perspective, CDC is funding this infrastructure and investing about \$9 million per year for that infrastructure, which then serves for the type of clinical trials that we're discussing.

Obviously, right now, those monies are encumbered and new trials will need to be adequately resourced. But at least there would not be a need to start up investment for the clinical trial capacity if you build on what already exists.

Donald McNeil: All right, thank you.

Conference Coordinator: Thank you.

And once again if you would like to ask a question, please press the star and 1 on your touchtone phone.

Yes, we just had someone queue up.

We'll take the next one from (Vivian Marks) with Chemical and Engineering. Go ahead, please.

(Vivian Marks): Yes, hi. I have a two-part question, if I may.

One, is it possible at all for you to give a figure, an estimate for the total cost for this first phase before you get to clinical trials, estimates for those four projects that you've outlined that you're going to be tackling next?

And the other question is a question for GSK perhaps but also for the others is, how difficult or how easy is it for a pharmaceutical company to decide to participate in this project?

G. Oosterbaan: I think we'll take the second question first and, David, maybe you can talk a little bit about GSK's participation in the partnership.

David Pompliano: Yes, indeed. This is Dave Pompliano speaking from GSK.

I think it was actually quite easy for us to enter in such an agreement. We have a great interest at GSK in participating and developing drugs. We're just doing our part to help develop drugs for the developing world.

I think it was best said by our CEO a number of years ago when he said he did not want to be the head of a corporation that caters only to the wealthy.

And so we have put in place a completely dedicated research site. We have put in place the support that we need from around and outside the corporation. And we have a commitment to bringing compounds into the clinic.

(Vivian Marks): Thank you.

G. Oosterbaan: And I think I'll have Mel Spigelman answer the first question now.

Mel Spigelman: I think the initial financial commitment from the TB Alliance is roughly of the order of about \$2.5 million a year to this research. And that will be a three-year process at least.

I think though that in terms of the total cost, it's difficult to estimate -- and this is due to issues that have been brought up already -- we're leveraging so many of the other resources that GSK brings which don't necessarily show up on a financial statement, so to speak.

So that even though we can quantify a part of our commitment and GSK has the similar certainly at least commitment within the facility at Tres Cantos, it really is a much greater financial commitment because of what David alluded to earlier -- whereby the high throughput screening, and other resources from GSK's facilities have really contributed tremendously to this project.

So I don't know, David, if you might want to say a few more words about those resources and what GSK is bringing to bear on that end.

David Pompliano: Right.

So I can only sort of reiterate what I said earlier that the Tres Cantos site is not operating in a vacuum. It is literally plugged into the machine, the drug discovery machine that GSK is. And that includes a number of support functions and other expertise areas, most particularly the high throughput screening facility, but not limited to that.

There was a whole group of the discovery researchers within GSK that work on development - producing proteins, doing X-ray crystallography, doing bioinformatics work, all the supportive work and the sort of target validation work that needs to be done in the early stages of the program.

We also have many discovery medicines - clinicians who are even now planning how we might bring compounds into the clinic and the type of trials we would envision. All that planning is going on in the background as well.

So, I think it is difficult to quantify exactly the number of people at GSK that are actually working on these projects. But I have to say it's considerable.

And the other thing I will add, actually being in the research area, is that there's a certain energy around these areas. And it's very easy to engage researchers from all different therapy areas around GSK in working on these diseases that I think it makes everybody feel like they're doing the right thing.

(Vivian Marks): Thanks very much.

Conference Coordinator: Thank you and we'll go next to the side of Donald McNeil with the New York Times.

Donald McNeil: Hi. I gather you don't have a long queue of questions waiting.

Dr. Pompliano, if any of these drugs turned out to have promise, is it likely that they will have crossover effects on another diseases? In other words, if they turn out to work against TB, are they also likely to work against other kinds of infection?

David Pompliano: Right.

Donald McNeil: And what are the, you know, what the advantages and disadvantages of that?

David Pompliano: Right.

So in some cases, yes; in other cases, no. For example the ICL, isocitrate lyase, it's unlikely to have a crossover effect on diseases other than TB. And of course, we are targeting the very specific TB enzyme so even if there were other organisms, and there are, that contain that gene, it's unlikely to have at least a dramatic effect on it.

So, that one I would discount as being - as not really being any more general.

The -I'm saying with the InhA protein as well, that's also a very specific enzyme in TB.

There are other analogs of that particular gene, basically the (unintelligible) gene in many other different bacteria. But again this particular mode of biosynthesis is very specific to bacteria. So again, it might have crossover; but, the way we're driving a chemistry program would be very specific to the TB organisms.

Now the pleuromutilin class is a drug spectrum agent and it does have activity against other bacteria like staf, strep, those community pathogens. And in fact, GSK is developing a different molecule for that indication.

But again, the goal here is to make the molecule that we're going to end up with, in this particular area, very specific for TB. And that means a lot of different things but not only specific for the TB bug in terms of efficacy against it but also as a formulation that might be required, the sort of, you know, the pharmacokinetic requirements, what you needed to treat a disease like TB.

Like - again, I think we are trying to be as careful as we can to tailor these molecules towards the TB organism.

Donald McNeil: If you end up - you might end up with two molecules that are related to each other but tailored in different ways so that one is almost going to be

specifically aimed at TB and assess it against TB while the other one is tested against staf, strep, things like that?

David Pompliano: Yes, I think that's probably the way it'll have to go.

Again, the treatment requirements for TB are much different, right? I mean, you're going to have it for a very long time. You're going to have to have maybe a different formulation that you either might have to have different types of pharmacokinetics.

So I would anticipate that they will be different molecules of the same class.

Donald McNeil: Yeah. All right thanks - I'm sorry.

Mel Spigelman: Donald, this is Mel.

Just to add a little bit to that, we have other programs with other classes of antibiotics that are used for non-TB infections. We have a macrolide program, a quinolone backup program, et cetera.

And at least in general, our experience has been that once you start to specifically modify those molecules for TB activity, you do begin to separate out the activities, the optimal activities for TB compared to whether it's strep or staf or other organisms.

So, certainly there's no guarantee of where research will go but at least it's been our experience that once you put the resources behind optimizing for TB, you do tend to get away from optimal cross activity, with other organisms.

So, it's a theoretical possibility, but my guess would be that once we have molecules from these programs, they probably won't be the same molecules that would be optimal for other infections.

Donald McNeil: Thank you.

Conference Coordinator: Thank you.

And once again if you would like to ask a question, please press the 1 followed by the 4 on your touchtone phone.

And at this time, we have no further questions. I'd like to turn it back to the moderating site.

G.Oosterbaan: Great.

So I just want to thank everyone again for joining us today. We've really seen a remarkable change in the TB drug pipeline as we've outlined today.

I just want to thank every one of our speakers -- Dr. David Pompliano, Dr. Ken Castro, Mark Harrington. And if you don't have anymore final remarks from any of you, we might have one more sign off from the Alliance.

Mark, David, Ken?

Man: No.

Man: No.

G. Oosterbaan: Okay, thank you.

Well, again, thanks everyone for joining us. We think that the kind of prospects for new improved TB treatment has really dramatically improved. And we're excited and looking forward to sharing more updates with all of you. And thank you for your interest in joining us today.

Thank you very much. Good-bye.

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