Meeting Report
1st Semi-annual Global TB Community Advisory Board Meeting

November 7-8, 2011
Arlington, Virginia, USA

TBCAB
GLOBAL TB COMMUNITY ADVISORY BOARD

Report: The First Meeting of the Global TB Community Advisory Board

I. The Global TB Community Advisory Board (TB CAB)

The Global TB Community Advisory Board (TB CAB) is dedicated to increasing community involvement in tuberculosis (TB) research and to mobilizing political will regarding key TB product development issues. The TB CAB is comprised of nine research activists from Portugal, Brazil, India, Kenya, Russia, South Africa, the UK, and the US who are extensively involved in HIV and TB research networks.

The broad goals of the TB CAB are to:

- Interact strategically with developers of TB drugs, diagnostics, and vaccines at key moments in the development process;
- Influence research and roll-out decisions of developers from a community perspective;
- Learn about the priorities and plans of the TB research world, then activate TB CAB members' networks to educate them and build an advocacy platform to influence the TB research community;
- Bring special attention to neglected populations – e.g. pediatrics, TB/HIV co-infection;
- Drive good quality research and accelerate/support regulatory approval processes; and
- Interact with TB research funders and policymakers to drive development and uptake of new TB tools.

II. Overview of the 2011 TB CAB Meeting

Treatment Action Group (TAG) convened the first meeting of the TB CAB on November 7-8, 2011 in Arlington, Virginia, USA. TAG planned the meeting, which focused on TB treatment research, to coincide with the annual Critical Path to TB Regimens[1] (CPTR) meeting. This timing facilitated the participation of drug sponsors and developers, who met with the newly formed TB CAB and presented their latest research plans, findings and access strategies for the TB new drugs being developed.

The objectives of the TB CAB meeting were to:

- Strengthen the TB research and regulatory science literacy of experienced HIV research and TB activists;
- Review the most current information on compounds and regimens being evaluated in clinical studies;

[1] The Critical Path to TB Drug Regimens (CPTR) initiative aims to speed the development of new and markedly improved drug regimens for tuberculosis. This partnership brings together the world's leading pharmaceutical and other drug developers, global regulatory agencies, and civil society organizations to support advances in regulatory science, the development of infrastructure, and other progress needed to facilitate the development and availability of new TB drug treatments. Co-founded by the Bill & Melinda Gates Foundation, the Critical Path Institute, and the TB Alliance and launched in March 2010, CPTR is working with stakeholders around the world to advance a new paradigm that dramatically speeds new TB drug regimens to patients.
Source: http://cptrinitiative.org/about/our-mission/

- Discuss with product developers their short- and long-term strategies for developing TB drugs and regimens;
- Identify key advocacy priorities that the TB CAB would like to address based on roadblocks in research, regulatory, or uptake of new products within programmatic settings; and
- Provide a community perspective to product developers and sponsors of drug research trials on their access issues and ethics.

On the first day of this two-day meeting, TB CAB members in attendance (see Table 1 for a complete list of meeting participants) participated in a variety of sessions designed to orient them to the history, current state, and key issues of TB research. Presentations led by TAG and Medical Services Corporation International staff gave an overview of the clinical pipelines for TB vaccines, diagnostics and treatment; the history of TB drug development and regulatory science; and challenges and opportunities for including children in treatment research. Participants discussed gaps and opportunities in the field of TB research, and strategized to create priorities for discussions with developers.

These discussions with TB drug developers were the focus of the second day of meetings. Clinical and community engagement representatives from the TB Alliance, Tibotec and Otsuka presented their development plans and access strategies. They then fielded questions and responded to concerns voiced by TB CAB members.

III. TB CAB meeting with the TB Alliance

Carl Mendel's Presentation
[Note: product development information may be outdated]

Dr. Carl Mendel, Senior Vice President for Research and Development at the Global Alliance for TB Drug Development (TB Alliance), centered his presentation on the TB Alliance's efforts to "efficiently bring to market affordable and easy-to-use regimens that shorten and simplify treatment" for drug sensitive (DS) and drug resistant (DR) TB. After giving an overview of the 20 discovery and one preclinical projects of the TB Alliance, he provided details on two novel combination studies. Dr. Mendel shared promising results from NC-001—the first novel combination early bactericidal activity (EBA) study—and plans moving forward to test the most promising combinations for both DS- and DR-TB. One such combination will be tested in NC-002, a serial sputum colony counting (SSCC) study with a two-week EBA sub-study, and the first study to examine DS- and DR-TB together using the same treatment.

Dr. Mendel went on to highlight issues with the current DR development path, including that using the 24+ month standard of care treatment as a control makes testing even much shorter new regimens lengthy. The TB Alliance is advocating for a new development paradigm in which "Drugs X, Y, and Z in combination are indicated for the treatment of tuberculosis caused by *M.tb* strains that are sensitive to drugs X, Y, and Z." Finally, Dr. Mendel gave an update to the Phase III REMoxTB Trial testing moxifloxacin to shorten DS-TB treatment. With sites in Latin America, Africa and Asia, the study was anticipated to complete enrollment in 2011 and results are expected in 2014.

TB CAB Discussion

Community Engagement in Research
In response to the TB CAB's questioning regarding plans for community engagement in studies beyond REMoxTB, the TB Alliance indicated that it would replicate REMoxTB's community advisory board structure in several NC-002 sites, adapting the research literacy materials to include DR-TB and other relevant items.

Pediatric TB
The TB CAB identified pediatric TB as a priority issue and inquired about timelines and plans for pediatric formulations for new products and the need for a clear Pediatric Investigation Plan (PIP). The TB Alliance responded that, due to risk-benefit issues, they would not study a new compound in children until Phase III trial data were available.

Concerns about Drug Resistant Study Arm Participants
There are three arms in the proposed 230 person, eight-week SSCC NC001 study[2] of Pa824-moxifloxacin-pyrazinamide (PaMZ): DS-TB patients will be randomized to either PaMZ or the standard of care, isoniazid-rifampicin-pyrazinamide-ethambutol (HRZE); while those with DR-TB (as defined by the use of the Hain Plus test, which detects some of the most common resistance mutations to isoniazid and rifampicin), will receive treatment on an open label basis. Samples will be gathered for drug-susceptibility testing (DST) with the Hain GenoType MTBDRsl polymerase chain reaction (PCR) test, which detects resistance to fluoroquinolones (FQs), ethambutol, and injectables – but has not been validated by the World Health Organization (WHO) for clinical use – and rapid culture (MGIT) for time-to-positivity (TTP) for Z. It is unclear how rapidly these latter resistance results will be available, but diagnostic delay could potentially expose participants with either FQ or Z resistance to suboptimal therapy and the emergence of resistance to the other old drug as well as to Pa-824.

Dr. Mendel stated that all multidrug resistant TB (MDR-TB) arm participants testing positive for resistance to Z will be considered late exclusions and provided with treatment in existing programs. He stated that TTP by MGIT could take approximately two weeks, which he did not think was long enough for suboptimal drug pressure to further amplify drug-resistant TB strains. The TB Alliance estimates that 50% of the MDR arm study subjects might have Z resistance – though TB CAB members pointed out that in Tibotec's recent open-label study results presented at Lille, about 70% of participants globally had signs of Z resistance. There is concern that DST for Z is not very accurate, so that even those resistant to Z may go unidentified and mistakenly receive the experimental regimen, leading to risk of developing further DR. At the subsequent CPTR meeting, additional questions were raised about the adequacy of the proposed Z resistance screening methods by Dr. Clifton Barry of the National Institute of Allergy and Infectious Diseases (NIAID), among others.

[2] Clinicaltrials.gov reference number NCT01498419; http://clinicaltrials.gov/ct2/show/NCT01498419?term=Pa-824&rank=4

Future Directions
When asked about plans for follow-up compounds in the same class as PA-824, the TB Alliance explained that PA-824 and TBA 354 – a preclinical nitroimidazole compound in the TB Alliance's portfolio -- are competing compounds, and whichever is more effective will move to Phase III trials. The NC-002 study is planned for early 2012, with a target enrollment of 230 patients at eight sites in South Africa, Brazil and Tanzania. The TB Alliance will continue exploring other promising drug combinations identified in NC-001 and in ongoing preclinical work as building blocks for new regimens.

Funding & Advocacy
The TB Alliance advocates for money for research and development for new TB drugs. It believes that when new regimens are available, sufficient resources may be obtained for delivery of new tools through funding bodies such as UNITAID and the US Agency for International Development (USAID). The TB Alliance said that it cannot raise funds for Phase III trials until Phase II data are available; however, if a very promising regimen is identified in Phase II studies, the TB Alliance representatives at the meeting expect to secure the approximate $75 million in funding required for Phase III trials. They estimate that an EBA study costs $4 million, and a SSCC study $10 million.

Issues for Advocacy
As described above, the TB Alliance would like to see a more streamlined, harmonized, even unified DS/DR development path with a shortened timeline for identifying treatment success. Dr. Mendel suggested that an appropriate endpoint would be relapse-free rates six months after treatment cessation. Discussion ensued on whether this would be acceptable for DR-TB, given the poor standard of care (though DS-TB might require a longer follow-up, and certainly a larger sample size, to demonstrate non-inferiority over the current, 95% effective standard of care HRZE). The TB Alliance also raised the issue of capacity in finding trial sites capable of doing EBA studies using the SSCC method. They suggested using TTP on liquid culture (MGIT) as an endpoint would enable more sites to participate in EBA studies, as TTP is easier to do than SSCC. However, some experts such as Dr. Barry feel that the TTP on MGIT may be a difficult technology to standardize across multiple sites.

IV. TB CAB meeting with Tibotec

Chrispin Kambili's Presentation
[Note: product development information may be outdated]

Dr. Chrispin Kambili, Senior Director of Infectious Diseases at Janssen Pharmaceutical Companies presented on TMC207, Tibotec's bedaquiline. Tibotec (now known as Janssen) is a subsidiary of Johnson & Johnson. Dr. Kambili presented detailed data about the bedaquiline's Phase I, phase II, and pharmacokinetic (PK) results, including that administration of nevirapine does not affect TMC207 exposure. He discussed the efficacy and safety data from multi-center, Phase II studies of patients with MDR-TB. The drug was safe and well tolerated, though QT prolongation was seen. There were, however, no pathologically prolonged (i.e. >500 msec) QT intervals, and no adverse events associated with the QTcF changes. Adding TMC207 to a five-

drug MDR-TB regimen resulted in a significantly faster median time to culture conversion compared with background therapy alone (12 weeks vs. 18 weeks), and in a significantly higher sputum conversion rate (79% vs. 58%). He then described the design of a Phase III superiority study projected to enroll 600 subjects with MDR-TB and pre-extensively drug resistant TB (XDR-TB), expected to start mid-2012, pending health authority review and approval.

Dr. Kambili dedicated a portion of his talk to pediatric plans and Tibotec's compassionate use (CU) program. For the former, Tibotec is exploring partnerships with the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Group of NIAID and the Pediatric Interest Group (PIG) of the Tuberculosis Trials Consortium (TBTC), and anticipates starting a pediatric clinical program in 2012, starting with the bioavailability study for the pediatric formulations. For the pediatric clinical trial (planned to start pending successful negotiations with IMPAACT, and availability of the protocol) Janssen plan to use a sequential age group approach to assessing PK and safety in children 0-2 years, 2-5 years, 5-12 years and 12-18 years, starting with the oldest first. Tibotec's CU program had 25 patients in 10 countries in Africa, South Asia, and Europe at the time of the presentation. Tibotec also recently initiated an expanded access program (EAP) clinical trial in Russia and Lithuania. Patients were limited by strict medical criteria to XDR and pre-XDR patients, and were treated at validated centers.

Regarding access, Tibotec has initiated discussions with the WHO about the prequalification process, rapid guidelines, and partnering opportunities with the Global Drug Facility (GDF). Tibotec is considering technology transfer to low-cost manufacturers in India. They anticipate taking distinct market access approaches according to geography and disease burden in high MDR-TB burden countries, the US and Europe, and other countries/regions. Tibotec plans to aim for some level of cost recovery; it is not planned to be a commercial business venture.

TB CAB Discussion

Regulatory Filing Plans
Tibotec stated that it plans for Health Authorities submissions in 2012 to request for provisional approval with data from the two Phase II studies. Tibotec first plans to file with the US Food and Drug Administration (FDA), then the European Medicine Agency (EMA). It will then prioritize subsequent submissions to high burden countries (Russia, China, India and South Africa). It was noted that Russia does not have to wait for EMA approval since it is not part of the European Union.

Access Issues
Though the CU program could potentially provide bedaquiline to many patients with pre-XDR in South Africa, there has not been sufficient uptake. There is a lack of familiarity with CU programs in South Africa. There is a need to educate the providers to take full advantage to save lives of those with limited treatment options.

Safety Concerns
The TB Alliance doesn't want to combine TMC207 with other drugs like moxifloxacin

associated with QT prolongation. Karen Manson of Tibotec indicated that data were currently insufficient to make the risk/benefit assessment in XDR populations. Tine de Marez added that this issue will be further explored in the Phase III study where FQs are allowed.

Pediatric TB
Tibotec is exploring a pediatric clinical program. TMC207 is difficult to formulate, not to manufacture. The molecule is not water-soluble which makes developing pediatric formulations challenging.

MDR Prophylaxis for Latent TB Infection of Close Contacts
The TB CAB raised the issue of why Tibotec had recently canceled a planned prophylactic trial proposed by the AIDS Clinical Trials Group (ACTG) Tuberculosis Transitional Science Group (TB TSG) for close contacts of MDR-TB cases. Dr. Kambili maintained that, while current data is limited on healthy (even if TB-exposed) individuals, once the drug is approved, the company will resume an open attitude towards the proposed trial. Dr. De Marez added that there is a concern about the risk/benefit in using the drug in healthy volunteers, particularly given the drug's long half-life and common drug-drug interactions.

Issues for Advocacy
Tibotec stated that the TB CAB could assist in:

- finding sites to help enrollment;
- advocating for regulatory flexibility to do different types of clinical trials;
- helping to determine post-marketing appropriate use;
- facilitating adoption in national guidelines; and
- speeding up the WHO prequalification process.

V. TB CAB meeting with Otsuka

The focus of the TB CAB meeting with Otsuka was on policy, access, and regulatory issues.

VI. Summary of Priority TB Drug Research Advocacy Issues

PK Combination Studies for bedaquiline and delamanid
CPTR focuses on developing new TB regimens, not individual TB drugs; however, bedaquiline and delamanid, both entering Phase III studies and likely to be used in conjunction in the field once approved, have yet to be studied together in PK studies. Otsuka and Tibotec must support PK studies to provide information on drug-drug interactions, and whether they are safe to use together. The EMA and FDA must also do their part to require that companies provide these data as a condition for accelerated approval, so they can be safely administered to the MDR-TB and XDR-TB patients who so desperately need better drugs.

Compassionate Use and Expanded Access Programs
Drug sponsors, regulators, providers, and national health authorities must work together to enable early access and CU of new TB drugs as they enter Phase III. Tibotec has already initiated and Otsuka is likely to initiate CU/EAPs. However, the path to providing people with

pre-XDR and XDR-TB with potentially life-saving investigational agents is poorly defined in many countries and needs education of regulators and providers so that patients with limited treatment options can fully benefit from these potentially life-saving programs.

Pediatric Investigational Programs

Developers and sponsors of new drugs and regimens need to create PIPs for new agents as they enter Phase III clinical trials, rather than waiting for Phase III data to be completed and moving into pediatrics sequentially. Over one million of the new TB patients each year are infants, children and adolescents, and they cannot afford to wait for lengthy Phase III trials to be completed. Lessons from the HIV pediatrics research should be used to develop a more ambitious and expedited research plan that addresses the need of pediatric TB patients.

Harmonization of Regulatory Agencies

Regulatory authorities need to harmonize their requirements for accelerated approval and to shorten the length of TB trials for new TB drugs and regimens; for instance, using time to culture conversion as an endpoint. The EMA has standards for such approval, while the FDA's stance is less clear. New drugs and regimens can shorten the time to culture conversion, but the process for their evaluation, approval and delivery will be lengthy unless authorities become more modern, flexible and harmonized.