TBCAB
GLOBAL TB COMMUNITY ADVISORY BOARD

Meeting Report
10th Semi-annual Global TB Community Advisory Board Meeting

14-15 July 2016
Durban, South Africa

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Advocating for future new TB drugs

Following members' initial expressions of interest in December 2015, the TB CAB discussed what phase II safety and efficacy data are necessary to feel comfortable advocating for the initiation of pre-approval access programs and phase III trials for future new TB drugs and regimens. To frame this discussion, Dr. Rada Savic, Assistant Professor in the Department of Bioengineering and Therapeutic Sciences at the University of California San Francisco (USCF), gave a presentation on the rationale for phase IIc studies in TB drug development. Several TB CAB members then led the group's discussion guided by six sub-questions, including: how we define phase III studies, what data were available for bedaquiline and delamanid before the initiation of Otsuka and Janssen's pre-approval access programs and phase III trials; what we want to know in the future before advocating for the initiation of pre-approval access programs and phase III studies and how to balance access to new drugs while maintaining a high standard of scientific rigor in research; what role phase IIc trials can play in helping to fill some of the knowledge gaps that currently exist between phase IIb and III trials; whether pre-approval access programs could be designed to help answer questions relevant to patients and programs; and how the availability of bedaquiline and delamanid affect our thinking on pre-approval access programs for future new TB drugs.

Clinical Trials and Protocol Review Training

Prof. Andreas Diacon, Director of TASK Applied Science at the University of Stellenbosch led a training on clinical training and protocol review. The training included an overview of key terms, the types of clinical trials and definitions of each phase, as well as the drug development timeline, using bedaquiline as a case study. Prof. Diacon compared the drug pipeline for TB drugs with those of other disease areas with more market appeal, such as cancers and cardiovascular diseases. Diacon also covered investment needs and existing incentives for innovation offered by bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Potential advocacy activities identified for the TB CAB to take forward included brokering support for TB drug research and harmonized and improved TB regulatory capacity in countries where new treatments are most needed.

Union Updates on STREAM I & II

Dr. Francesca Conradie, Principal Investigator at Sizwe Hospital, provided the TB CAB with an update on the STREAM study, stage 1 of which compares the 9-month "modified Bangladesh" regimen (nine months of moxifloxacin, clofazimine, ethambutol and pyrazinamide, supplemented by high-dose isoniazid, kanamycin, and prothionamide for the first four months) to the 18 to 24-month WHO standard MDR-TB treatment regimen. Stage II is a RCT serving as Janssen's phase III study, and will evaluate whether bedaquiline can replace the injectable agent, kanamycin, or reduce the duration of treatment from nine to six months.

Francesca updated the TB CAB on the status of each of the study sites participating in phase II of the STREAM trial, and discussed the potential impacts of, and the Union's concerns regarding anticipated uptake of the 9–12 month shortened regimen under program conditions in countries with STREAM II sites given the regimens endorsement in the 2016 WHO MDR-TB treatment guidelines. Francesca relayed the Union's plans to discontinue enrollment to Arm A, the standard 18-24 month regimen at sites in countries implementing the shortened regimen. The TB CAB pushed back reiterating the importance of continuing enrollment to arm A in STREAM II until results from STREAM I are available as the modified Bangladesh regimen has yet to be proven non-inferior to the WHO standard of care. Francesca stressed the anticipated logistical challenges of procuring drugs for the 24-month regimen in a country implementing the shortened regimen under program conditions. She noted particular concern with the continued procurement of cycloserine given that it is not a component of the shortened regimen. In addition, Francesca raised concern about the trial's ability to retain participants randomized to the 24-month regimen when a shortened regimen is available to them outside of the trial. Francesca highlighted some additional future implementation considerations for the regimens under study, including access to ECG machines, and the need for increased production of clofazimine and scale-up of second-line drug-sensitivity testing.

Beyond the efforts under taken to establish a STREAM CAB in Mongolia, Francesca and Ezio described the Union's plans to implement the STREAM Community Engagement Plan at all trial sites from 2016 to 2021. Ezio Tavora and REDE-TB will lead the development of site-level community engagement programs. This work consists of health authority sensitizations, community organization mapping exercises, and consensus- and capacity-building workshops.

South African Medical Research Council Perspective: Research Funding for TB and HIV

The TB CAB met with Glenda Gray, President and CEO of the South African Medical Research Council (SA MRC), who expressed the MRC's commitment to conducting research efficiently and effectively. Glenda explained how the MRC research budget can be broken into two main categories: social determinants of health (40 percent) and biomedical research (60 percent). She then reviewed the portfolio of research projects the MRC is funding, including those related to drugs, diagnostics, vaccines, and devices for HIV, TB, malaria, non-communicable diseases, and maternal and child health. Glenda raised concern about an impending seven percent decrease (ZAR38 million) in funding for 2017/18. Glenda noted that when funding decreases, science shrinks, highlighting the necessity of continued lobbying to maintain and expand government investments in science.

Glenda and the TB CAB then discussed how communities can help advocate for increased investments in research. Glenda encouraged use of an investment case that demonstrates the benefits of scientific research and how investment in innovation improves country wealth to off set the view of science as a luxury investment, and not as an element contributing to the alleviation of poverty. Glenda also encouraged establishing a unified voice regarding the benefits of science among civil society groups and government

agencies, including National Departments of Health and National Departments of Science and Technology.

Otsuka

Jeffrey Hafkin, Director of Novel Products within Otsuka's TB Unit provided an update on Otsuka's research program for delamanid, including an overview of several ongoing and planned studies most of which are being led by external researchers and networks. Jeffrey noted Otsuka's plans to lock the database for its phase III trial of delamanid in December 2016, to analyze the data in 2017, and to submit results for publication in a peer-reviewed journal in 2018. Jeffery also mentioned Otsuka's recent provision of data from its pediatric PK and safety study to the WHO, which is expected to issue guidance on the use of delamanid in children down to six years old before the end of 2016. The TB CAB encouraged Otsuka to also submit the available pediatric data to the EMA so that delamanid's label might be updated to include populations less than 18 years of age.

Switching the discussion over to the access program, Jeffrey explained Otsuka's compassionate use and expanded access programs, and its donation to MSF. Jeffrey also highlighted delamanid's availability via the Global Drug Facility to 100 low and middle-income countries eligible for TB financing through the Global Fund. Jeffrey concluded his presentation with an overview of recently completed and planned regulatory submissions, including delamanid's approval in Hong Kong in March 2016 and Otsuka's submissions of NDAs in Indonesia in August 2015, Turkey in April 2016, and the Philippines in June 2016. Jeffery also informed the TB CAB that additional dossiers are being prepared for submission in China, Peru and Vietnam; and that Ostuka is working to identify local partners to enable registration and commercialization in India, Russia, Eastern Europe, and South Africa.

Sanofi:

Isabelle Cieren-Puiseux, Senior Manager in the TB Program; Gavin Bauer, Head of External Affairs, South Africa; Rashem Mothilal, Country Head of Medical, South Africa and Jacob Smit, Sanofi Pasteur, Vaccines Department attended this session of the TB CAB meeting, which covered a broad range of topics, including the BCG vaccine shortage, linezolid access and pricing in South Africa, and details of the company's research and access programs for rifapentine.