Meeting Report
5th Semi-annual Global TB Community Advisory Board Meeting

October 28–29, 2013
Paris, France

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TB Markets

The group discussed with Andrew Jones (Bill & Melinda Gates Foundation) & Harkesh Dabas (Clinton Health Access Initiative) recent tuberculosis (TB) drug stock-outs and access issues, such as in India and Romania. Andrew and Harkesh identified issues with the second-line drug market especially, and how their pilot program plans to work on both the demand and supply side to address these issues in a few countries. The TB CAB identified the following related advocacy needs, including: pushing for simplified regimens in country to prevent market fragmentation; holding countries accountable for increasing the numbers of patients on treatment; encouraging Global Fund to simplify grant and procurement processes for countries; and ensuring public and private sector integration.

Vaccine Updates and Advocacy

Michele Tamaris (South African TB Vaccine Initiative) presented on the current TB vaccine landscape and highlighted SATVI's community engagement endeavors. Jennifer Wooley (Aeras) updated the group on Aeras's vaccine advocacy plans, which the TB CAB stressed should include community input in study designs and broader research agendas, rather than just at the trial site level. The group also discussed how differing messages on projected funding needs for vaccines from different stakeholders creates confusion among donors and advocates.

Clinical Trial Design and Statistics

Jason Stout (Duke University) adapted a presentation from Caroline Sabin to give an overview of clinical trial design and statistics to the TB CAB. Jason covered different types of studies and how to interpret results. For some TB CAB members, this was new information and for some, it was a refresher.

PanACEA Studies

The CAB's first meeting with this European-funded network, Norbert Heinrich's presentation introduced the group to the PanACEA's high-dose rifampicin studies. HIGHRIF1, a 2-week study going up to 35mg/kg of rifampicin, found that high doses were safe and well-tolerated. HIGHRIF2, a 2-month study going up to 15 and 20mg/kg, will have results shortly. A first analysis also shows that the higher doses are equally safe. The PanACEA is conducting a Multi-Arm Multi-Stage (MAMS) adaptive phase IIb trial, looking at several combinations of drugs (including SQ109, moxifloxacin, and high doses of rifampicin). Pediatric PK work would begin once adults are ready to enroll in phase III. PanACEA follows a policy of establishing accessible pricing arrangements with drug IP holders who have their drugs evaluated in PanACEA studies. The TB CAB and PanACEA agreed to collaborate for community input on future protocols and informed consent development.
[Note: product development information may be outdated]

Bedaquiline

Chrispin Kambili, Tine De Marez, Daniel De Schryver (Johnson & Johnson) discussed the challenges they've experienced initiating a phase III trial, based on delayed and mixed

health authority feedback; the TB CAB stressed the importance of conducting this trial. J&J shared that pediatric formulations (granules and dispersible tablets) are progressing well, but the collaborative pediatric study with IMPAACT has yet to start as a result of continued discussions and lengthy protocol development timelines. The compassionate use program has been working well—some 250 patients have accessed bedaquiline so far. The TB CAB expressed concern over strict pricing requirements in the U.S. which require TB programs to purchase a full 6-month supply up front to receive the public sector discounted price; J&J says they are working with the U.S. Centers for Disease Control and Prevention, and drug distributor MetroMedical to ensure that public-sector pricing discounts are available to those purchasing even less than a full 6-month course of drug in the U.S. The TB CAB noted that a study needs to be done on integrase inhibitors and bedaquiline drug-drug interactions.
[Note: product development information may be outdated]

QuantiFERON-TBGold

Masae Kawamura (Qiagen) met with the TB CAB in response to a letter the TB CAB had sent over concerns regarding Qiagen's marketing of their TB infection test in India, where TB infection is not diagnosed or treated (the test does not accurately diagnose active TB). Masae indicated that there is no active marketing of QFT in developing countries and detailed Qiagen's actions in response to accusations of misuse, including: caution labels on product boxes, caution statements on QFT laboratory reports, commercial partner staff trainings on ethical use and QFT limitations, and promotion of the RNTCP guidance on "Stopping malpractice of TB diagnosis". Masae shared slides from the customer training slide deck that cover ethical use and limitations of QFT in addition to an advisory letter that is now part of the welcome dossier for all new customers. Qiagen requires all distributors in India to sign an ethical use statement and continues to engage the RNTCP and key opinion leaders on the issue. The TB CAB held firm that the risk for misuse of the test is higher than any potential benefit, and the test should be removed from the Indian market.
[Note: product development information may be outdated]

Delamanid

Jeffrey Hafkin, Marc Destito, Larry Geiter, Patrizia Carlevaro (Otsuka) updated the TB CAB that Otsuka's phase III trial was due to finish enrollment in November 2013. Decisions from the European Medicines Agency and the Japanese regulator (PMDA) were pending. The pediatric study was enrolling the eldest cohort at the time of the meeting. Otsuka did not reveal pricing plans (other than that they plan a tiered-pricing scheme) but say they will prioritize access for countries in the clinical trials. The TB CAB impressed upon Otsuka that waiting for registration before initiating compassionate use is unacceptable, especially as patients with extensively drug-resistant TB are excluded from the phase III trial (they were included in phase II).
[Note: product development information may be outdated]

Pediatric Panel

Steve Graham (University of Melbourne), Babis Sismanidis (World Health Organization) and James Seddon (Imperial College) discussed with the TB CAB how pediatric TB could be brought into the context of child survival. We don't know the true burden of disease; children are often an afterthought and left out of both clinical trials and operational

research; to integrate services, we need to know the numbers yet to know the numbers we need to integrate services to scale up detection. In the meantime, we could at least have better data on how many kids are on treatment (if not how many kids don't ever access it, which is the true burden). Lack of a good diagnostic tool is the central roadblock, but even without it we could do better. Guidelines for Xpert use in children are similar to guidelines for use in adults, though any sputum-based test has limitations for kids (stool/urine are not yet validated, a blood test would be ideal). Clinicians should treat kids empirically, especially as children tolerate drugs better than adults. The EMA has been clear that NOT including children in studies is unethical, and the Helsinki Declaration has been reworded so that it is unethical to exclude children from trials. The WHO published the first pediatric estimates in 2012, but should still mandate that countries notify pediatric cases (disaggregate based on age/sex).

TB Alliance

Stephanie Seidel and Elizabeth Gardiner (TB Alliance) met with the TB CAB. We ran quickly through the topline NC003 results, which showed that clofazimine does not have early bactericidal activity either alone or in combination, and that bedaquiline+Pa-824+pyrazinamide was the most effective combination in this two-week study. If successful, REMoxTB would be the first new regimen in 50 years (topline results will be available in 2014—the TB CAB thinks they should publish their rollout experience). Moxifloxacin is not on the Essential Medicines List for TB; some countries care about this more than others. The TB Alliance is interested in working on normalizing community engagement for cross-trial work. Regarding pediatrics, their UNITAID-funded STEP TB project focuses on getting two manufacturers for a fixed-dose combination for first-line drugs dosed for children, then determining the right dose for HRZ in kids under 5kg.
[Note: product development information may be outdated]

AZD5847

Scott Butler (AstraZeneca) led AstraZeneca's first meeting with the TB CAB about their oxazolidinone drug in development, AZD5847. AZ has 250 scientists working in infectious disease in Boston and Bangalore, and say they have no commercial aspirations for compound AZD5847. AZD5847 is active intracellularly, which linezolid is not; it's probably safer also in terms of peripheral/optic neuropathy. AZD5847 is safe in animals when given for 90 days. There is increased exposure when given with food. It has little potential for drug-drug interactions. They expect phase IIa study results in April 2014. It will be tested in phase IIb with 4-5 combinations, starting in mid-2014 ideally. The TB CAB encouraged AZ to think about use of the drug for LTBI. AZ was interested in soliciting the CAB's opinion on phase III designs.
[Note: product development information may be outdated]