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EATG European AIDS Treatment Group

TO: Marco Cavaleri, European Medicines Agency (EMA)
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Edward Cox, U.S. Food and Drug Administration (FDA)
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Cc: Margaret Hamburg, FDA
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Chrispin Kambili, Janssen Pharmaceuticals
Tine de Marez, Janssen Pharmaceuticals
Andrew Nunn, Medical Research Council Clinical Trials Unit, University College London
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July 28, 2014

RE: Concerns regarding STREAM stage II trial design for bedaquiline approval

Dear Dr. Cavaleri and Dr. Cox,

We are writing to raise serious concerns with the design of a proposed extension to the STREAM study as a confirmatory trial of bedaquiline's safety and efficacy. A rigorous phase III trial is essential for fulfilling the conditions of the accelerated approval of bedaquiline from the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA).[1,2] It is our understanding that both the EMA and FDA have indicated to Janssen Pharmaceuticals that the proposed STREAM stage II trial is an acceptable design.

[1] Food and Drug Administration (U.S.). Postmarketing Requirements and Commitments: Sirturo (bedaquiline). 2013 August 9. Silver Spring: Food and Drug Administration (U.S.) Available from: http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm. (Accessed 2014 July 28)
[2] European Medicines Agency. Summary of the risk management plan (RMP) for Sirturo (bedaquiline). 2014 May 6. London: European Medicines Agency. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Risk-management-plan_summary/human/002614/WC500162201.pdf. (Accessed 2014 July 28)

Our key concern is that the design of STREAM II assumes that the original STREAM I trial will show that the so-called modified Bangladesh regimen is non-inferior to the current World Health Organization (WHO) standard of care for the treatment of multidrug-resistant TB (MDR-TB).[3] As you know, this experimental regimen is based on a shortened regimen of multiple drugs only tested in observational studies, only one of which has been published to date in peer-reviewed literature and was severely flawed. The modified Bangladesh regimen is markedly different from both the WHO and the U.S. Centers for Disease Control and Prevention (CDC) recommended strategy for treating MDR-TB, and cannot be recommended before being tested in any randomized controlled trials (hence the need for STREAM I).[4,5,6] Assumptions about the modified Bangladesh regimen's non-inferiority over the current standard of care are therefore necessarily speculative. We therefore find it problematic that a regulatory authority could agree with such an assumption. If STREAM I fails to show the modified Bangladesh regimen's non-inferiority to the current standard of care, hundreds of patients in STREAM II will have been enrolled meaninglessly in a scientifically unsound and unethical study comparing bedaquiline-containing arms to an unacceptable regimen.

We have raised these concerns with the drug and study sponsors, and urged them to continue the enrollment of the WHO standard of care arm throughout STREAM II, or at least until an adequate interim analysis of STREAM I data are available to provide confidence in the modified Bangladesh regimen's non-inferiority over the standard of care. However, both defer to alleged support from EMA and FDA of this flawed design.

We fear the EMA and FDA's laxity in allowing an experimental regimen to serve as a control arm for a registration trial of a new drug jeopardizes good science and ethical research, and sets a dangerous precedent for future TB trials. We understand the logistical and scientific challenges posed by comparing shorter experimental regimens with the current standard of care, including that continued enrollment for the standard of care arm will delay study results by over a year. Nevertheless, we strongly believe that the choice between potentially less valuable and ethically problematic data fifteen months earlier, or guaranteed useful results slightly later, is an obvious one.

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[3] Frick M. Fool's Errand: The Sloppy Science of the MDR-TB STREAM Trial. TAGline. 2014 Spring. Available from: http://www.treatmentactiongroup.org/tagline/2014/spring/fool%E2%80%99s-errand-sloppy-science-mdr-tb-stream-trial. (Accessed 2014 July 28)

[4] World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update. Geneva: World Health Organization, 2011. Available from: http://www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/en/. (Accessed 2014 July 28)

[5] American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of tuberculosis. In: Centers for Disease Control and Prevention (U.S.). MMWR Recomm Rep [Internet]. 2003 Jun 20;52(RR-11):1–77. Table 16: Potential regimens for the management of patients with drug-resistant pulmonary tuberculosis. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm#tab16. (Accessed 2014 July 28)

[6] World Health Organization. The use of short regimens for treatment of multidrug-resistant tuberculosis [Internet]. 2012 August 10 (cited 2014 July 28). Available from: http://www.who.int/tb/challenges/mdr/short_regimen_use/en/.

In this context, we request urgent clarity on the following three questions:

1. What happens to STREAM II should STREAM I fail to show the modified Bangladesh regimen's non-inferiority to the current standard of care?

2. Does a failure to adequately address this issue amount to a violation of medical ethics, given that the control group in STREAM II has not been validated to be non-inferior to the current standard of care?

3. Should STREAM stage I fail to show non-inferiority, will the EMA and FDA keep Janssen to their deadlines for submitting phase III data (2021 and 2022, respectively)?

We thank you for your timely response to this important issue. Please direct responses to: Erica.lessem@treatmentactiongroup.org

Best,

The AIDS Treatment Activists Coalition (ATAC)
The Community Research Advisors Group (CRAG)
European AIDS Treatment Group (EATG)
The Global TB Community Advisory Board (TB CAB)