EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Mrs. Erica Lessem
European AIDS treatment Group
Place Raymond Blyckaerts, 13
B-1050 Brussels, Belgium
e-mail: erica.lessem@treatmentactiongroup.org

26 September 2014
EMA/477974/2014
Human Medicines Evaluation Division

RE: Sirturo (bedaquiline) EMA/H/C/002819
Concerns regarding STREAM stage II trial design for bedaquiline approval

Dear Mrs. Lessem,

Thank you for your letter from 28 July 2014 in which you raise several concerns with regard to the design of the STREAM study as a confirmatory trial of safety and efficacy for Sirturo (bedaquiline). The European Commission has issued on 5 March 2014 a positive decision which granted Sirturo a conditional marketing authorisation valid throughout the European Union. As mentioned in the approved annex II of Sirturo, as a specific obligation, the marketing authorisation holder will perform a safety and efficacy study of bedaquiline in different treatment regimens compared to a regimen that does not include bedaquiline (confirmatory phase III study) following an agreed protocol. At the time of the marketing authorisation, the difficulties and uncertainties related to the design of this study were acknowledged and discussed with the applicant and within the regulatory network. Factors that were considered included the need to explore efficient ways of using bedaquiline within optimised regimens, as well as the need to allow adequate interpretation of the safety results in the context of feasible studies. Based on these elements the proposed design of the modified STREAM trial was considered acceptable. Importantly the study as planned would contribute to clarifying the safety profile of bedaquiline much earlier than a sequential approach in which the results of the STREAM 1 studies would be awaited before starting the second phase. Based on initial proposal, it would provide interim results by 2018 and final results by the end of 2021. We understand that you have been discussing the protocol with the Sponsor and further modifications have been introduced. The revised protocol is currently under discussion at the EMA.

With regard to your specific 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?**

   At present we cannot speculate on the outcome of the STREAM I trial, but we can reassure you that those results will be discussed by the CHMP and appropriate actions will be considered as needed. From a regulatory perspective the results from STREAM II would be expected to be still informative under any possible scenario arising from STREAM I outcome.

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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?**

   The STREAM II protocol actually evaluates two bedaquiline-containing regimens:

   - one with a 40-week duration (identical to the modified Bangladesh regimen) in which kanamycin is substituted by bedaquiline (and levofloxacin replaces moxifloxacin) and
   - a simplified (in terms of the number of medicines used) and shortened 28-week regimen (the intensive treatment phase is limited to 8 weeks, instead of the 24-weeks in the WHO regimen, and a continuation phase limited to 20 weeks, instead of 48-72 weeks).

   We believe that the results generated by the bedaquiline-containing arms will provide very useful information on the efficacy and safety of Sirturo in a timely manner, according to the specific obligation requested by the CHMP. Enrolment of patients in such trial has to be in conformity with clinical trials legislation in the participating countries expectedly providing adequate level of review of ethics aspects.

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)?**

   EMA will work closely with the MAH in order to determine whether there is a need for reconsidering the deadlines.

Yours sincerely,

Marco Cavaleri
Head of Anti-infectives and Vaccines
Scientific and Regulatory Management Department