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June 12, 2012

Dear Members of the Global Tuberculosis Community Advisory Board,

RE: Open letter dated May 24, 2012 regarding Pharmacokinetic Studies, Paediatric Studies, and Compassionate Use of Bedaquiline

Thank you for sharing with us your concerns pertaining to the bedaquiline (TMC207) development programme and for giving us an opportunity to respond. We certainly share your vision of accelerated availability of new TB treatments that will improve outcomes for patients. Please allow me to address your concerns in turn.

Pharmacokinetic studies:
Janssen and the Global Alliance for TB Drug Development (TB Alliance) have completed a two week EBA/DDI study with a model compound from the same general chemical class as delaminid in which no DDI was observed (the NC-001 study, which combined bedaquiline and PA-824) (IUATLD, 2011, Everitt *et al*).

In addition, Janssen has had informal discussions with Otsuka on the need to evaluate the safety of our two compounds, bedaquiline and delaminid, in combination. The recent publication of delaminid's efficacy and safety data offers us a great opportunity to ask the right questions regarding a bedaquiline/delaminid drug-drug interaction study. We are committed to sharing information and to working with partners to ensure the safe use of bedaquiline.

However, it is important to highlight some of the challenges such a study might present. It is likely that a two week PK study in healthy volunteers will not provide the information needed to ensure the safe combination use of these two agents due to: (1) the long half life of bedaquiline; (2) the nature of the metabolites and their impact on the safety profile; and (3) amount of time it takes, at least for bedaquiline, to reach steady state. A much longer and complex trial, most likely in MDR-TB patients, will be required to obtain the necessary information. As you know, in general, health authorities are reluctant to approve studies involving more than one investigational agent, especially when the compounds in question have just started phase 3 trials. Nonetheless, we will continue to pursue this need to understand potential interactions between drugs that could end up in the same patients at the same time. We will keep you apprised of our discussions with Otsuka and with the health authorities on this issue.

Paediatric studies:
We are committed to conducting paediatric studies with the right partners. Our Paediatric Investigational Plan (PIP) has been approved by the European Medicines Agency (EMA) and we

have been in an ongoing dialogue with the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) and the TB Alliance on the PIP. A protocol is being proposed by IMPAACT. We will make every effort, taking into account all necessary safety precautions, that the proposed sequential recruitment of paediatric age cohorts is accelerated wherever possible.

Compassionate use and early access programmes (CU/EAP):
The current regulatory framework prohibits us from taking any action which could be viewed as promoting our CU/EAP. We strongly believe that if Janssen were to disseminate a list of potential TB care providers, treatment programme implementers and institutions, and TB centers of excellence, we would be violating the essence of those regulations. It has been our hope that advocates who are aware of our CU/EAP would reach out to groups such as the Green Light Committee or to national TB programs as these entities are likely to have information regarding capable MDR-/XDR-TB treatment program implementers. Our criteria for CU/EAP simply require that healthcare facilities be recognized by the national TB programme as being capable of providing treatment for (pre) XDR-TB in accordance with local (national) and international standards.

Rescue study and treatment of XDR-TB:
We also acknowledge your request to participate in discussions about a rescue study involving multiple new investigational compounds in patients with XDR-TB, as is being proposed by the TB Alliance. As you know, Janssen and the TB Alliance are working together in partnership to accelerate the availability of new TB drug regimens. TB Alliance have indicated to us that most of the drugs that are being proposed for inclusion in rescue therapy regimen are at least a year away from having available the minimal safety data (i.e., at least 2 months of use in TB patients) needed to move such a study forward. It might be worth pointing out that lack of access to companion drugs, including WHO Group 5 drugs, is at the moment one of the greatest impediments to appropriate treatment of patients with XDR-TB. WHO has been urged to do what it can to improve the availability of Group 5 drugs, which are currently not available through the Global Drug Facility.

We trust that you will agree that we are taking appropriate action to address the issues you have raised. We look forward to working with you to assure improved access and treatment outcomes for MDR-TB patients, while ensuring the appropriate use of TMC207.

Yours sincerely

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Global Medical Affairs Leader, Infectious Diseases

cc: Myriam Haxaire, Karen Manson, Tine De Marez