TO: Dr. Chrispin Kambili
CC: Dr. Myriam Haxaire-Theeuwes
Ms. Karen Manson
Dr. Tine de Marez
Janssen Pharmaceutical Companies of Johnson & Johnson
700 US Highway 202 South
Raritan, NJ 08869

24 May 2012

Open Letter Re: Pharmacokinetic Studies, Paediatric Studies, and Compassionate Use of Bedaquiline

Dear Dr. Kambili,

Thank you for meeting with the Global Tuberculosis Community Advisory Board (TB CAB) in November 2011. We hope that this will be the first of many productive meetings. We were pleased to hear that the development plans for bedaquiline are going well and we are writing to re-emphasise a number of issues that arose from the meeting.

The TB CAB remains concerned that the two new investigational tuberculosis (TB) drugs which are farthest along in development, bedaquiline and the Otsuka agent delamanid (OPC6783) -- both of which are being studied in people with MDR-, pre-XDR, and XDR-TB,[1] and both of which are entering phase III studies and have or are likely to be submitted to regulatory authorities this year -- have not been studied together in the pharmacokinetic (PK) studies that will tell us how they interact and whether they are safe to use together.

However, when they are approved, it is inevitable that they will be used together in the field because people with XDR-TB desperately need effective new oral drugs to shorten their time to culture conversion, and hopefully, cure.

Therefore, we ask you and Otsuka to support the necessary PK studies to demonstrate whether the drugs are safe to use together. We understand from our discussions that it may be complicated to make the appropriate agreements between the two companies to conduct the necessary studies with the two investigational agents yourselves. If this is the case, we call on you to work with a third party such as the AIDS Clinical Trials Group or the TB Alliance, to ensure that sufficient data are available to inform guidance for the appropriate use of the two drugs in combination, once they are both approved.

[1] MDR-TB: multi-drug resistant TB; XDR-TB: extensively drug resistant TB

We are also requesting that the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) require that the companies provide these data as a condition for accelerated approval.

Secondly, we understand that your paediatric studies will begin this year and that you will be studying the drug in infants, children and adolescents in de-escalated age bands from 18 down to 0 years to characterise PK for dose selection for each of four cohorts (0 months to < 2 years; ≥ 2 to < 5 years; ≤ 5 to <12 and ≤12 to <18 years) with a total of approximately 60 participants.

As cohorts are recruited sequentially beginning with the oldest age band -- and proceeding to the next cohort down in age can only take place upon the availability of adequate PK and safety data (at least eight weeks of the study drug in the case of bedaquiline) – we ask you to ensure that, taking account of all necessary safety precautions, this process is accelerated wherever possible and transition to the next cohort occurs before recruitment of the older cohort is complete.

As paediatric drug development is so novel, and previous agents have not been studied in this way, we understand that guidance for Paediatric Investigational Plans (PIPs) is unclear, and will remain so until several drugs have undergone such studies and regulatory requirements may be subject to change. For example, we heard in a subsequent ECAB meeting with the EMA, that children ≥ 10 years might be included in adult studies. Overall we call on you to make sure that this population, -- particularly the youngest age group -- does not have not wait several years to benefit from new TB drugs, already approved for adult use, as happened in the early days (and still sometimes happens) with HIV drug development.

Finally, the TB CAB would also like to support Janssen in the roll out of its laudable ongoing compassionate use (CU) and expanded access program (EAP). Given the TB CAB's global scope, we can help encourage quality care providers in various countries to take advantage of these opportunities. To assist in scaling up your CU/EAP program to enable more pre-XDR and XDR patients to benefit from bedaquiline access, we request that Janssen provide a list of potential providers, implementers, institutions and centers of excellence you would recommend we encourage to apply for your CU/EAP programs. We also encourage Janssen 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. Additionally, please indicate the point person (and contact information) within Janssen with whom it would be best for the TB CAB to coordinate its CU/EAP advocacy efforts.

Please direct your response to the TB CAB regarding these concerns to Erica.lessem@treatmentactiongroup.org. We look forward to receiving your response at your earliest convenience.

Yours truly,

Polly Clayden, United Kingdom
Colleen Daniels, Australia
Nathan Geffen, South Africa
Denis Godlevskiy, Russian Federation
Mark Harrington, United States
Giselle Israel, Brazil
Bactrin Killingo, Kenya
Blessina Kumar, India
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for the Global Tuberculosis Community Advisory Board (TB CAB)