TO: Dr. Patrizia Carlavaro
CC: Dr. Lawrence Geiter
Dr. Davide Manissero
Otsuka
3 Rue du Marché
1204 Geneva
Switzerland

21 May 2012

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

Dear Dr. Carlavaro,

We thank Otsuka 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 of your filing for delamanid (OPC67683) approval with the European Medicines Agency (EMA). As your plans for development progress, 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, delamanid and the Janssen investigational agent bedaquiline (TMC207) -- 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 Janssen 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.

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

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

Secondly, we understand that Otsuka intends to study delamanid in children, is developing a powder formulation for the youngest age groups, and will submit a Paediatric Investigational Plan (PIP) to the EMA in late summer of this year.

We ask that you begin studying the agent in children before the phase III trial is completed in adults, and that you will study the drug in infants, children and adolescents. We expect that you will conduct studies in de-escalated age bands from 18 down to 0 years to characterise PK for dose selection for each of age group.

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 -- 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 when sufficient PK data is obtained in the older cohort (likely 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 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 $\geq$ 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.

Additionally, the TB CAB would like to support Otsuka in its laudable plans to develop a compassionate use (CU) or expanded access program (EAP) to provide individuals with or at great risk of developing XDR-TB with access to potentially life-saving therapy. We appreciate Otsuka's concerns regarding the challenges of identifying quality providers of care in the absence of a global company infrastructure. As such, the TB CAB offers its global reach and expertise in assisting Otsuka in developing a list of criteria for participation in its CU/EAP. Additionally, the TB CAB can encourage identified quality providers, implementers, institutions and centers of excellence in a range of countries to participate in these programs once developed. We request therefore that Otsuka involve the TB CAB in its discussions of CU/EAP plans. We also encourage Otsuka 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. Please confirm whether Martin Pan will be the point person with whom the TB CAB can 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
Erica Lessem, United States
Khairunisa Suleiman, South Africa
Ezio Tavora dos Santos Filho, Brazil
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for the Global Tuberculosis Community Advisory Board (TB CAB)