Otsuka
Otsuka-people creating new products for better health worldwide

Geneva, June 15, 2012

TO: The Global Tuberculosis Community Advisory Board (TB CAB)

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
Wim Vandevelde, Belgium

Re: Your open letter, "Pharmacokinetic Studies, Paediatric, and Compassionate Use of Delamanid", 21 May, 2012

Dear TB CAB Board Members,

Thank you for your recent open letter, 2012. Like you, we share the same long-term goal of maximizing patient benefits and achieving TB elimination. We believe that frank and sustained dialogue among all stakeholders - public and private - is essential for advancing this mission.

As you know, Otsuka has been extremely committed to advancing its clinical development programme for tuberculosis and was pleased to share safety and efficacy results from our Phase IIb study (Trial 204), recently published in the *New England Journal of Medicine* (http://www.nejm.org/doi/full/10.1056/NEJMoa1112433). Results from the trial showed a statistically significant 53% increase in sputum culture conversion (SCC) after two months between study subjects receiving delamanid 100 mg twice-daily (BID) plus a background regimen (BR) consistent with WHO treatment guidelines compared with subjects receiving placebo plus BR alone.

With the release of this data, Otsuka also provided one of the most comprehensive and transparent disclosures of scientific data in the industry including release of all adverse events, concomitant medications and treatment history along with disclosure of the full study protocol. The majority of adverse events recorded in the study were mild to moderate. Study subjects receiving delamanid plus BR experienced a higher incidence of QT prolongation on electrocardiogram than those receiving placebo plus BR. None of the QT interval prolongations were associated with any clinical manifestations such as syncope or arrhythmias.

We believe these findings may represent a major step forward for the TB community which has not seen a new treatment option in nearly half a century. In addition, a long-term, open-label surveillance study is underway to extend the efficacy and safety findings from the Phase IIb study and further assess whether sputum conversion is sustained throughout treatment and correlates to favourable outcomes at the end of treatment.

Otsuka SA
3, Rue du Marché
1204, Geneva
Switzerland

As you rightly point out, Otsuka has initiated an international, randomised, controlled Phase III trial of delamanid in study subjects with MDR-TB, including those with co-existing HIV infection and taking antiretroviral therapy. Simultaneously, we are committed to ensuring MDR-TB patients in need of novel therapies will have access to delamanid as soon as possible, which is why we have filed a Marketing Authorization Application (MAA) with the European Medicines Agency (EMA). As you will note from the Phase IIb results published in the NEJM, SCC at two months was selected as an established measure of successful treatment and we appreciate your support for this as a valid clinical endpoint.

Furthermore, you raised a number of salient points in your letter of May 21 which we would like to address here:

1) There is no question that drug-resistant TB patients, including MDR and XDR-TB, are in urgent need of new, effective treatment regimens. To this end, we are considering PK studies between delamanid (OPC-67683) and bedaquiline (TMC-207). In fact, representatives from Otsuka and Janssen are in communication with one another to clarify issues regarding basic CMC/quality information and data, safety and PK profiles. Following such an exchange and digestion of information, we will be able to better determine if it is appropriate to conduct a co-administration study of these compounds and how such a study may be designed.

   We are certain you would agree that when introducing new drugs, the safety of prospective patients must be paramount. This is our most important priority and the reason why ensuring safety and efficacy profiles are in line with regulatory requirements must be a prerequisite for future drug-drug interaction (DDI) studies.

2) With regards to your questions concerning our Paediatric Investigation Plan (PIP), we must first clarify a few inaccuracies cited in your letter. A PIP has already been submitted and received a positive opinion by EU authorities in November 2011. (Details: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/pips/EMEA-001113-PIP01-10/pip_000797.jsp&mid=WC0b01ac058001d129)

   Five studies are included in the PIP which includes:

   Study 1: An oral suspension for delivery primarily to infants and children aged birth to 5 years. This is on track with validation studies of a proposed paediatric formulation already under way.

   Study 2: A 10-week juvenile repeat-dose toxicity and toxicokinetic study in rats. This study is under way.

   Study 3: An open-label, randomised, single-centre, single-dose bioequivalence trial to compare delamanid suspension to delamanid 50 mg tablets in healthy adults. This study will be conducted after completion of study 1 and is required prior to recruiting younger children and infants in studies four and five.

   Study 4: An open-label, uncontrolled, multi-centre pharmacokinetics and safety trial of delamanid in children from birth to less than 18 years of age with MDR-TB. The protocol for this study is under review. There will be a single protocol for all age groups so that we can move as quickly as possible. The first age group will include adolescents 12-17 years of age inclusive and we will use the existing tablet formulation for this study. The next age group will include those 6-11 years of age using the tablets now used for adults and the paediatric formulation followed by the youngest age groups. The protocol for this study is under review.

Otsuka SA
3, Rue du Marché
1204, Geneva
Switzerland

Study 5: A six-month, open-label extension trial of study 4 to evaluate long-term safety/tolerability, efficacy, and pharmacokinetics of delamanid in children from birth to less than 18 years of age with MDR-TB. The protocol for this study is under review.

3) As you may already be aware, Otsuka is considering potential approaches and models of compassionate use and expanded access. The company is currently in discussions with European regulatory bodies and other stakeholders to develop a rational compassionate use program. These discussions are on-going while we work to develop a safe and effective protocol that may be reviewed and approved by all relevant parties.

   In today's changing healthcare environment, private industry and regulatory agencies are more committed than ever to applying necessary pharmacovigilance, particularly concerning new compounds. This is extremely important for Otsuka, which is why a very stringent safety follow-up has been included in our study. With regulatory requirements changing at a rapid pace, there are few stakeholders well experienced in the latest safety surveillance, making the development of a new and comprehensive safety protocol a clear priority. Once we have finalized our plan - which will be consistent with the guidance we receive from some EU regulatory institutions - we will be glad to schedule a briefing with interested TB CAB members.

4) With regards to your request for Otsuka participation in a rescue study for XDR-TB patients, we are not familiar with this study and have not received any requests for collaboration on this topic prior to your letter. Nevertheless, as such a study you describe would involve the use of multiple newly developed compounds, we believe this issue is integrally linked to the issue of appropriate DDI studies as referenced above in point 1. Once again, ensuring the safe and responsible use of new drugs requires the blessing of necessary regulatory authorities. Following the first MAA approval of delamanid, Otsuka may consider participation in a rescue study as a follow-up or add-on to a potential DDI study.

Finally, with regards to your question as to whom within Otsuka may serve as a focal point for compassionate use/expanded access advocacy efforts, Otsuka SA is responsible for centralizing the company's public health, advocacy and communication activities and should be your point of contact on all issues. We will then be glad to put you in touch with the relevant individuals based on the issue area.

Thank you once again to each TB CAB member for your continued interest and support of our work in TB. Otsuka's commitment to TB innovation represents the culmination of hard work and persistence for over thirty years. We are now entering an exciting and promising phase and look forward to continued collaboration with you and many other partners as we move forward.

Best regards,

Dr. Patrizia Carlevaro
Managing Director

Otsuka SA
3, Rue du Marché
1204, Geneva
Switzerland