Timing is everything for compassionate use of delamanid

To the Editor:

Nature Medicine recently published a News article[1] that I believe requires some clarification; the article describes difficulties in early patient access to Deltyba (delamanid), a new antituberculosis drug that received conditional approval by the European Medicines Agency late in 2013. The title of the story refers to the drug's developer, Otsuka Holdings, as a "nutraceutical company." Otsuka Pharmaceuticals, which is owned by Otsuka Holdings, is the 20th-largest pharmaceutical company in the world by total sales (http://www.pmlive.com/top_pharma_list/global_revenues), and it produces pharmaceuticals such as the blockbuster antipsychotic Abilify.

It is worth noting that both Sirturo (bedaquiline), the drug the Californian patient Gary in the story was already receiving, and Deltyba cause a significant prolongation of the cardiac QT interval in some people receiving them[2,3], and there is reason to be very concerned that the two together may amplify this effect. On the basis of preclinical animal data from related compounds, there is also some reason to believe that the two drugs may actually antagonize each other's action[4]. These are among the issues that led the World Health Organization in 2013 to issue interim guidance for Deltyba that did not recommend the use of this agent in combination with Sirturo until additional studies had been done[5].

The article focuses on Otsuka's compassionate-use program and an individual patient's heartbreaking story. Patient access to new medications in early clinical development is always a difficult and sensitive issue. Deltyba is approved for use in adults with multidrug-resistant tuberculosis in Europe, but the US Food and Drug Administration has not yet approved it. The European Respiratory Society and the World Health Organization implemented a virtual consulting system for difficult-to-manage tuberculosis cases in 2013 (https://www.tbconsilium.org). This consilium had an important role in developing Otsuka's compassionate-use program and leading tuberculosis physicians have agreed that the overall strategy was appropriate[6].

Nearly 45% (213/481) of patients in Otsuka's phase 2B trial of Deltyba received a 6-month treatment extension that amounted to compassionate use. In addition, Otsuka has also launched a phase 3 trial and completed randomization of 511 patients, about 340 of whom are receiving Deltyba (ClinicalTrials.gov; NCT01424670).

Finally, the article compares the number of patients treated through the compassionate-use program of Sirturo and Deltyba, but it fails to note that Sirturo was approved in the US in 2012, whereas Deltyba was only approved in the EU late in 2013 and is still not approved in the US. Everyone wants to ensure that patients with life-threatening drug-resistant tuberculosis gain access to these new therapeutic options as quickly as possible, but it must be done safely and in a controlled setting. Otsuka has made a huge contribution to global tuberculosis control in bringing this new drug forward. We cannot, and should not, risk compromising patient safety by rushing forward carelessly. There will be a time for vastly expanded access to this new agent, but that time is not now.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

Clifton E Barry III
Tuberculosis Research Section, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland, USA.
e-mail: cbarry@niaid.nih.gov

1. Gruber, K. *Nat. Med.* **21**, 103 (2015).
2. Guglielmetti, L. *et al. Clin. Infect. Dis.* **60**, 188–194 (2015).
3. Gler, M.T. *et al. N. Engl. J. Med.* **366**, 2151–2160 (2012).
4. Tasneen, R. *et al. Antimicrob. Agents Chemother.* **55**, 5485–5492 (2011).
5. World Health Organization. *The Use of Delamanid in the Treatment of Multidrug-Resistant Tuberculosis: Interim Policy Guidance* (WHO/HTM/TB/2014.23) (World Health Organization, 2014).
6. Esposito, S. *et al. Eur. Respir. J.* **44**, 811–815 (2014).