mg twice daily) than to the lower dose (100 mg twice daily). Excess paresthesia, anxiety, and tremor in delamanid-treated subjects were uncommon but were felt to warrant continued pharmacovigilance. In animals, alterations in red blood cell production (rats), inhibition of vitamin K-dependent coagulation (rabbits), and dose-dependent liver histopathological changes (dogs) have been observed, but only at supraclinical doses (European Medicines Agency, 2013).

6b. Pretomanid

Pretomanid causes small reversible serum creatinine elevation (by about 0.2 mg/dl on average in healthy subjects after 8 days of a high pretomanid dose). This increase does not indicate a true change in renal function but appears to result from inhibition of renal tubular creatinine secretion (Ginsberg *et al.*, 2009a).

No pattern of treatment-associated adverse events was observed in phase IIa trials (Diacon *et al.*, 2010; Diacon *et al.*, 2012). In the phase IIb trial of pretomanid, moxifloxacin, and pyrazinamide involving 207 patients, pretomanid at the highest dose (200 mg/day) was associated with higher probabilities of experiencing grade 3 or 4 treatment-emergent adverse events (37%) and of discontinuing treatment due to adverse events (19%) than the lower (100 mg/day) pretomanid-dosed group (30% and 13%) or the standard-regimen control group (25% and 12%). The adverse events that occurred more frequently in one or both of the pretomanid-treated groups than in the control group included arthralgia (29% in pretomanid 200 mg, 33% in pretomanid 100 mg, 19% in controls), cardiac disorders (10%, 2%, and 5%, respectively), increase in AST or ALT to > 3 times the upper limit of normal (18%, 17%, 12%), nausea (13%, 23%, 12%), diarrhea (5%, 7%, 5%) epileptic seizure (2%, 0%, 0%), and agranulocytosis (2%, 0%, 0%) (Dawson *et al.*, 2015).

Among the cardiac adverse events associated with pretomanid, no treatment-emergent instances of QTcF > 500 ms were observed, but QTcF increased by an average of 18 ms in patients receiving 200 mg pretomanid, and 7% of the patients receiving this higher dose experienced QTcF increases of 60 ms or greater (Dawson *et al.*, 2015).

7. CLINICAL USES OF THE DRUG

7a. Use of delamanid in treatment of multidrug-resistant tuberculosis

Delamanid is currently approved in the European Union and Japan for treatment, as part of appropriate combination regimen, of MDR-TB in adult patients who otherwise lack an effective treatment regimen because of resistance or intolerability. The approval in Europe is conditional, and additional trial results are forthcoming.

Delamanid should be used only as part of an appropriate combination regimen containing at least two to three other active agents, in order to prevent development of resistance to delamanid. In clinical trials, it was evaluated together with a background MDR-TB regimen, and delamanid resistance emerged within 2 months in some patients whose background regimen was insufficiently active and potent, most commonly due to extensive drug resistance (World Health Organization, 2014; European Medicines Agency, 2015).

Efficacy of delamanid for tuberculosis has been evaluated in phase II trials, and phase III trial results are forthcoming. A 2-week study of early bactericidal activity first showed that delamanid lowered sputum bacterial counts in smear-positive non–MDR-TB subjects (Diacon *et al.*, 2011). Delamanid was then evaluated in combination with a clinician-selected optimized background regimen in a randomized, placebo-controlled trial (Study 204) of 481 adult pulmonary MDR-TB patients (Gler *et al.*, 2012). The proportion of patients who achieved the primary outcome—namely sputum culture conversion by day 57—was significantly higher in the subjects treated with delamanid plus optimized background regimen (45% and 42% with sputum culture conversion for doses of 100 mg twice daily and 200 mg twice daily, respectively) than in those receiving placebo plus optimized background regimen (30% sputum culture conversion). Delamanid also increased 2-month culture conversion among the subset of subjects who had XDR-TB at baseline (7/16 subjects with delamanid vs. 1/10 subjects who received placebo) (Gupta *et al.*, 2015b).

Two subsequent extensions of the above-described 2-month trial evaluated longer duration of therapy and later outcomes. A voluntary 6-month open-label continuation study (Study 208) of delamanid at a physician-chosen dose, in which 213 subjects participated (without randomization, and only offered to some patients at some study sites), observed a higher proportion of sputum culture conversion among those subjects receiving a total of ≥ 6 months of delamanid (130/143, 91%) compared to ≤ 2 months of delamanid (112/158, 71%) (Skripconoka *et al.*, 2013). Although promising, these phase II trial results were felt by the European Medicines Agency to be an insufficient demonstration of efficacy for an MDR-TB treatment indication for several reasons, including (1) selection bias among patients who opted to continue delamanid beyond 2 months obscures the ability to evaluate outcomes beyond 2 months in the randomized study, and (2) the higher proportion of XDR patients randomized to the placebo group may inflate the true benefit of delamanid. In addition, the studies were considered an insufficient basis for preferring a 100-mg twice daily dose (i.e., for concluding that 200 mg twice daily is above the threshold for maximum efficacy) because of selection bias in the clinical decision to escalate some patients' doses in the extension phase of the study (European Medicines Agency, 2013).

As a result of the conditional approval decision from the European Medicines Agency, a phase III trial of delamanid (clinical trial NCT0142) is currently underway to confirm the efficacy of delamanid in MDR/XDR-TB patients. In this multi-site trial, a total of 511 adult patients have been randomized to either delamanid (100 mg twice daily for 2 months, followed by 200 mg once daily for 4 months) or placebo for 6 months, for the first 6 months of an 18- to 24-