

## **CROI 2019 PRESS CONFERENCE ABSTRACTS**

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#### **QT EFFECTS OF BEDAQUILINE, DELAMANID OR BOTH IN MDR-TB PATIENTS: THE DELIBERATE TRIAL**

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#### **Background:**

Bedaquiline and delamanid are the first drugs of new classes approved for tuberculosis (TB) in 40 years. Both are oral, well-tolerated, and recommended for treatment of multidrug resistant (MDR) TB by WHO. However, these drugs and/or their metabolites have long half-lives, and each prolongs the QT interval with maximum effects weeks after drug initiation. The cardiac safety of these drugs given together as part of multidrug therapy has not been established.

#### **Methods:**

AIDS Clinical Trials Group (ACTG) A5343 is a phase 2, open-label trial randomizing adults with MDR-TB receiving multidrug background treatment (MBT) 1:1:1 to receive bedaquiline (BDQ arm), delamanid (DLM arm) or both (BDQ+DLM arm) for 24 weeks. Patients with QTcF >450ms or CD4 count < 100 cells/mm<sup>3</sup> were excluded. HIV-infected participants received dolutegravir-based ART. Clofazimine was not allowed, and levofloxacin was given in place of moxifloxacin. Three electrocardiograms (ECG) were performed at baseline, every two weeks for 24 weeks, then week 28. QTcF (in ms) was calculated by a core laboratory blinded to treatment. The mean QTcF change from baseline (averaged over weeks 8-24) was defined in each arm, and the QTcF change in the BDQ+DLM arm was compared to QTcF changes in the BDQ and the DLM arms. Grade 3 QTcF prolongation was defined as >500ms or >480ms with increase from baseline >60ms. Grade 4 was life-threatening dysrhythmia.

#### **Results:**

Eighty-four participants were enrolled in South Africa and Peru. The majority (75%) were men; median age was 34 years; 37% were HIV-positive. Changes in QTcF from baseline, by week, including 4 weeks after stopping study drugs, are shown in the Figure. There were no Grade 3 or 4 QT interval prolongation events. Among 74 participants with QTc data (2062 unique ECGs, 688 visits, 69 participants with data through week 20, 64 with data through week 24), preliminary mean (95.1% CI) on-treatment QTcF value (in ms) was 410.3 (403.0, 417.7)(BDQ arm), 413.5 (406.1, 420.8)(DLM arm) and 412.5 (405.0, 420.0)(BDQ+DLM arm). Mean (95.1% CI) change (ms) in QTcF from baseline was 11.9 (7.4, 16.5) in the BDQ arm, 8.6 (4.0, 13.2) in the DLM arm, and 20.7 (16.1, 25.4) in the BDQ+DLM arm.

#### **Conclusion:**

The combined effect on the QTcF interval of co-administration of bedaquiline and delamanid is clinically modest and no more than additive. This study demonstrates the cardiac safety of the combined use of these drugs in patients with MDR-TB taking MBT with normal baseline QTcF values.