Title: Evaluation of QT Prolongation During Bedaquiline Treatment Using a Time-Varying Tuberculosis-Specific Correction Factor (QTcTBT)

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Introduction: While bedaquiline is a part of first-line treatment of multidrug-resistant (MDR) tuberculosis (TB) [1], its metabolite, M2, is associated with QTc prolongation [2]. Assessing QT liabilities in TB patients is challenging due to tachycardia, which compromises the accuracy of the Fredericia correction[3, 4]. This challenging can lead to misdiagnosis of QT prolongation and unnecessary interruptions of treatment [5]. Earlier model-based analyses addressed this non-drug-related secular trend QTcF by estimating a time-on-treatment effect on QTcF [4, 6, 7]. However, this approach requires skilled personnel and is unsuitable for clinical practice. Our previous work found that TB-related tachycardia normalized with treatment, which led us to proposed a time-varying QT correction method (QTcTBT) to adjust for heart rate changes [8]. We aimed to evaluate the time-on-treatment effect and the robustness of the M2 effect estimation on QTc using QTcTBT instead of QTcF.

Method: Data from 429 patients with MDR-TB were collected from two Phase IIb trials. In C208, a randomized, double-blind, placebo-controlled study, newly diagnosed patients received BDQ or a placebo for 8 weeks (Stage 1) and 24 weeks (Stage 2) [9, 10]. In C209, a single-arm, open-label trial, newly diagnosed and treatment-experienced patients received BDQ for 24 weeks [11]. All patients received a background regimen. M2 concentrations at time of ECG measurement was derived using a published PK model and the observed PK data[12]. The QTcTBT model, adapted from a published exposure-QTcF model [6], consists a time-on-treatment effect on QT, circadian cycles, the M2 effect, and patient covariates. To evaluate the time-on-treatment effect, three models were compared: *i)* no time-on-treatment effect, *ii)* with a time-on-treatment effect but no systematic shift (allowing individual changes but not population-level changes), and *iii)* with both time-on-treatment effect and a systematic shift (allowing changes at both the population and individual levels). The M2 effect on QTc was also assessed. Parameter uncertainty and confidence intervals (CI) obtained via sampling importance resampling (SIR) [13]. Ten-fold cross-validation with ten repetitions was performed predictive performance. Software used included NONMEM 7.5, PsN 5.3.0[14], and R 4.2.2.

Results: Cross-validation showed that models with time-on-treatment effects performed similarly, whether assuming no systematic shift (normalized OFV 0, 95%CI -6.5 - 6.5) or with a systematic shift (OFV -5.2, 95%CI -5.6 - 4.8), while the model without time-on-treatment effects performed the worst (OFV +283.5, 95% CI 280.1 - 286.9). The model with a time-on-treatment effect but no systematic shift was selected. The Emax model best described the M2 effect, showing consistency across models. At a therapeutically relevant M2 concentration of 326 ng/mL, QT prolongation was 7.007 ms (90%CI 5.947 - 8.163) with a time-on-

treatment effect but no systematic shift. This finding from the QTcTBT model aligns with the 7.928 ms (90% CI 6.844 - 9.262) from the previous exposure-QTcF model.

Conclusion: This study demonstrated that QTcTBT, compared to QTcF, addresses the non-drug-related secular trend in QT and simplifies the quantification of BDQ's QT prolongation. The QT prolongation due to M2 at therapeutically relevant concentrations was robust across models and remained below 10 ms.

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