# QTc Prolongation with *Rukobia*

## Summary


- Clinically meaningful corrected QT (QTc) interval prolongation was not found with a therapeutic dose of *Rukobia* (fostemsavir [FTR]) 1200 mg once daily in a clinical study.[1] However, a supratherapeutic dose of 2400 mg twice daily was associated with significant max concentration- ($C_{max}$) driven QTc interval prolongation.
- Through 96 weeks of the BRIGHTE study, a total of 7 patients discontinued due to reaching protocol-specified QTc prolongation stopping criteria with 4 reported as non-serious and 6 out of the 7 patients continuing dosing with FTR outside of the study.[2] No cases of Torsades de Pointes (TdP) were reported.
- FTR should be used with caution in patients with a history of QT interval prolongation, when co-administered with a drug that has a known risk of TdP, or in patients with relevant pre-existing cardiac disease.[3,4]
- Important safety information is found in the attached Prescribing Information.


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## CLINICAL DATA

### Hruska et al.

A randomized, double-blind, placebo-and active-controlled, balanced cross-over study was conducted to evaluate the effects of FTR on the QT/QTc interval in healthy subjects.[1] A total of 60 subjects were randomized 1:1:1:1 to receive four 7-day treatments including FTR 1200 mg once daily, FTR 2400 mg twice daily, placebo (Days 1-6) and moxifloxacin 400mg (active control, Day 7 only), or placebo twice daily; separated by 10-day washouts.

No clinically meaningful effect on the QTc interval was observed with FTR 1200 mg once daily as the maximum mean time-matched placebo-adjusted QTc change from baseline based on Fridericia's correction method (QTcF) was 4.3 milliseconds (below the clinically meaningful threshold of 10 milliseconds [msec]).[1] Conversely, with a QTcF interval value of 11.2, FTR 2400 mg twice daily was associated with a clinically meaningful and statistically significant QTc prolongation.

FTR 1200 mg once daily was generally well tolerated with one AE leading to discontinuation (grade 2 diarrhea).[1] FTR 2400 mg twice daily was associated with one serious AE (headache) and four AEs leading to discontinuation (grade 1 and 2 vomiting, grade 2 headache, and grade 1 generalized rash).

The dose selection of 600mg twice daily in the phase 3 BRIGHTE study was based on an integrated approach, and in part considered the safety data from this QTc study.[2] Using simulations from the concentration-response (CP-ddQTcF) model, the maximum concentration at which the upper 90% confidence interval for ddQTcF will remain below 10 msec is 7500 ng/mL.[5] A $C_{max}$ of 7500 ng/mL equates to 4.2-fold the geometric mean $C_{max}$ following the FTR dose of 600 mg twice daily in the BRIGHTE study.

### BRIGHTE Study

This is an ongoing, partially-randomized, placebo-controlled, double-blind, phase 3 trial designed to evaluate the efficacy and safety of FTR in HTE patients with multi-drug resistant HIV-1.[2] Patients were failing their current regimen (HIV-1 RNA ≥ 400 copies/mL) and enrolled into 1 of 2 cohorts, according to their remaining treatment options. At baseline, those with ≥ 1 antiretroviral (ARV) drug in at least 1 but no greater than 2 ARV classes were randomized (Day 1 to Day 8) to add either FTR 600 mg twice daily or placebo to their failing regimen (randomized cohort). Patients with no fully active, approved

ARV options received open-label FTR and optimized background therapy (OBT) on Day 1 (non-randomized cohort). Beginning on Day 9, the randomized cohort also received open-label FTR and OBT.

Through Week 96, a total of 7 patients (7/371, 1.9%) discontinued the study due to reaching protocol-specified QTc prolongation stopping criteria (ie, confirmed QTcF >450 msec in males and >470 msec in females) with 4 reported as non-serious and 6 out of the 7 patients continuing dosing with FTR outside of the study at the request of their care provider through the FTR early access program.[2] Another 8 patients reported an event from the TdP Standardized MedDRA query (SMQ) – a broad coding term that includes other events such as QTc prolongation and syncope – but continued FTR treatment uninterrupted. There were no actual TdP episodes reported in the BRIGHTE study. Mean changes in QTcF from baseline to Week 24 and Week 96 in the randomized cohort and the non-randomized cohort were 2.0 (n = 241) and 1.2 (n = 183) and 2.9 (n = 88) and 9.2 (n = 50), respectively.

## DRUG-DRUG INTERACTIONS AND PRECAUTIONS

FTR should be used with caution in patients with a history of QT interval prolongation, when co-administered with a drug that has a known risk of TdP (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, or sotalol), or in patients with relevant pre-existing cardiac disease.[3,4] Drug-induced QT prolongation may be more prevalent in elderly patients.



**Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.**

**In order for ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 877–844–8872. Please consult the attached Prescribing Information.**

**This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.**


## REFERENCES

1. Hruska MW, Savant IA, Anderson JA, et al. Thorough QT/QTc trial to evaluate the effect of the HIV-1 attachment inhibitor BMS-626529, administered as its prodrug, BMS-663068, on QTc intervals. Presented at the 15th International Workshop on Clinical Pharmacology of HIV Therapy, May 19-21, 2014, Washington DC. Presentation P_54.
2. Data on File. Study 205888 (NCT02362503). ViiV Healthcare Study Register. Study entry at: https://www.viiv-studyregister.com/en/study/?id=205888.
3. ViiV Healthcare. Global Data Sheet for fostemsavir, Version 04, July 1, 2022.
4. Moore K, Mageau AS, Magee M, et al. Fostemsavir drug-drug interaction profile, an attachment inhibitor and oral prodrug of temsavir, for heavily treatment-experienced HIV-1 infected patients. Presented at IDWeek 2019, October 2-6, 2019, Washington DC. Poster 2500.
5. ViiV Healthcare, Module 5.3.5.3, Integrated Summary of Safety for fostemsavir, version 3.0, March 13, 2021.