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Evaluation of the impact of lopinavir/ritonavir (LPV/r) and ritonavir (RTV) on QTcF: results of a thorough QT study

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Purpose of the study

Literature reports suggest prolongation of QTcF may rarely occur in patients receiving antiretroviral therapy for HIV disease. We report a Phase I, multiple-dose, open-label, placebo- and active-controlled (moxifloxacin 400 mg QD), randomized study conducted according to a crossover design.

Methods

Study drugs were dosed for three days to achieve maximal exposure, as RTV-mediated CYP3A4 inhibition is complete and induction is minimal at Day 3. LPV/r was administered at 400/100 mg BID and at supratherapeutic dose of 800/200 mg BID. RTV was dosed at 400 mg BID. Digital EKGs were performed in triplicate on Study Day 3 and compared to time-matched baseline. No effect on QTcF was concluded if the 95% upper confidence bound for the difference of drug mean from placebo mean was less than 10 msec for all times of measurement (Per ICH Guidance). Pharmacokinetic samples were obtained and exposure and QTcF relationship was analyzed.

Summary of results

Substantially higher LPV (30–50% higher for 400/100 mg BID and 3-fold higher for 800/200 mg BID) and RTV (2-fold higher) concentrations were achieved on Study Day 3 compared to clinical doses of LPV/r 400/100 mg BID and RTV 600 mg BID at steady-state. At these increased concentrations, no effect on QTcF was noted with LPV/r 400/100 mg BID with maximum upper bound 95% CI of 6.3 msec; no effect on QTcF was noted with RTV 400 mg BID with maximum upper bound 95% CI of 7.6 msec; slight QTcF prolongation was observed with supratherapeutic 800/200 mg BID with maximum upper bound 95% CI of 15.8 msec.

Conclusion

Based on exposure-QT response modeling, the maximum concentrations observed with recommended QD or BID doses of LPV/r are lower than exposures predicted to result in a 10 msec increase in QTcF. LPV/r and RTV administered at approved doses does not result in clinically significant changes in QTcF.