

Poster presentation

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

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Purpose of the study

PR prolongation has been reported with HIV protease inhibitors such as atazanavir. We evaluated the potential for PR prolongation with LPV/r and RTV.

Methods

Phase I, multiple-dose, open-label, placebo-controlled, randomized study conducted according to a crossover design. Study drugs were dosed for 3 days to allow for maximal exposure, as RTV-mediated CYP3A4 inhibition is complete and induction is minimal. LPV/r was dosed at 400/100 mg BID and at supratherapeutic 800/200 mg BID. RTV was dosed at 400 mg BID. Digital EKGs and pharmacokinetic samples were obtained on study Day 3. Absolute PR interval on Day 3 and change from baseline were evaluated. Exposure-PR response modeling was performed.

Summary of results

Substantially higher LPV (30–50% for 400/100 mg BID and 3-fold for 800/200 mg BID) and RTV (2-fold) concentrations were achieved on Study Day 3 compared to historical steady-state values of LPV/r 400/100 mg BID and RTV 600 mg BID. Mean PR changes from baseline ranged from 11.6–24.4 msec (LPV/r 400/100 mg BID), 22.0–31.2 msec (LPV/r 800/200 mg BID) and 11.0–24.0 msec (RTV 400 mg BID), all $p < 0.0001$ compared to placebo. No subject had a PR interval greater than 286 msec. No subject experienced 2nd or 3rd degree atrioventricular block.

Conclusion

Based on the exposure-response model, it is estimated that the mean PR effect plateaus and has reached its maximum with the supratherapeutic 800/200 mg BID dose. At steady state, LPV/r is expected to produce clinically insignificant increases in PR interval of 18 to 20 msec and low dose ritonavir (100–400 mg daily) is expected to prolong PR by 4.8 to 11.6 msec. LPV/r and RTV do not result in clinically significant increases in PR interval. However, this effect should be considered when co-administering LPV/r or RTV with other drugs known to prolong PR interval or in patients with co-morbid conditions.