

Gilead GS-9350 Protease Inhibitor Booster

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from Jules: GS-9350 could be considered for boosting HCV protease inhibitors.

GS-9350, the "pharmacoenhancer" from Gilead Sciences, boosted the protease inhibitor (PI) atazanavir as well as ritonavir in a crossover study involving 42 healthy volunteers [1]. Gilead has already bundled GS-9350 with tenofovir/emtricitabine and its integrase inhibitor, elvitegravir, which until now relied on ritonavir for a pharmacokinetic kick [2]. The 4-in-1 pill, QUAD, is smaller than the 3-in-1 combo of efavirenz, tenofovir, and emtricitabine. QUAD is in a phase 2 trial.

Like ritonavir, GS-9350 strongly inhibits CYP3A. Gilead's booster appears not to threaten lipid metabolism and has properties that could make coformulation with other drugs simpler [2]. Gilead investigators tested that last proposition in a prelude to the ongoing phase 2 trial comparing atazanavir plus 150 mg of GS-9350 with atazanavir plus 100 mg of ritonavir--both with tenofovir and emtricitabine--in previously untreated people.

All healthy volunteers took once-daily atazanavir for 10 days with 100 mg of ritonavir, for 10 days with 100 mg of GS-9350, and for 10 days with 150 mg of GS-9350 in one of seven sequences [1]. Researchers measured atazanavir levels at the end of each 10-day stint, then the volunteers took 4 days off and returned for the next 10-day interval. Everyone took their drugs with a meal of about 400 kcal containing 13 grams of fat. The group included 28 men and 14 women, 28 whites, 10 blacks, 3 Asians, and 1 native American. Their ages averaged 28 years and ranged from 18 to 45.

Thirty-three people (79%) completed the study. Five dropped out because of adverse events, 2 withdrew consent, and 2 stopped at the investigator's discretion. The clinical problems that caused dropouts were all grade 2 in severity: anemia with atazanavir/ritonavir, paresthesia with atazanavir/ritonavir, and 3 rashes with atazanavir/GS-9350 (2 at 100 mg and 1 at 150 mg). All rashes resolved when the drugs stopped.

Total bilirubin rose by an average 3.1 mg/dL with 100 mg of GS-9350, 4.1 mg/dL with 150 mg of GS-9350, and 4.2 mg/dL with 100 mg of ritonavir. There were no changes in alanine aminotransferase, aspartate aminotransferase, or gamma glutamyl transferase. ECG showed no differences between GS-9350 and ritonavir in PR interval changes (3 people had grade 1 PR interval prolongations with all three treatments). There were no clinically relevant changes in QTcF or QRS intervals.

Atazanavir area under the concentration-time curve (AUC), maximum concentration,

trough concentration, elimination half-life, and time to maximum concentration were nearly identical with 150 mg of GS-9350 and 100 mg of ritonavir. Atazanavir trough was lower with 100 mg of GS-9350 than with ritonavir (837 versus 1340 ng/mL), as were maximum concentration (4420 versus 5270 ng/mL) and AUC (45,100 versus 55,200 ng/h/mL). Elimination half-life was shorter with 100 mg of GS-9350 than with 100 mg of ritonavir (9.7 versus 15.7 h), and time to maximum concentration slightly longer (3.5 versus 3.0 h).

The Gilead team proposes that 150 mg of GS-9350 "may be a suitable alternative to ritonavir for boosting atazanavir."

References

1. Ramanathan S, Warren D, Wei L, Kearney BP. Pharmacokinetic boosting of atazanavir with the pharmacoenhancer GS-9350 versus ritonavir. 49th ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy). September 12-15, 2009. San Francisco. Abstract AI-1301.
2. Xu L, Liu H, Murray BP, et al. Discovery of GS-9350: a novel pharmacoenhancer without anti-HIV activity. 49th ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy). September 12-15, 2009. San Francisco. Abstract H-934.