Pharmacokinetic Boosting of Atazanavir with the Pharmacoenhancer GS-9350 versus Ritonavir

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Introduction

• GS-9350 is a specific, potent, mechanism-based inhibitor of human cytochrome P450 3A4 (CYP3A) enzymes without antiviral activity.
• GS-9350 increases (boosts) plasma exposures of the CYP3A4 probe midazolam and the HIV integrase inhibitor elvitegravir to allow comparability to ritonavir (RTV).
• Boosted-atazanavir (ATV) is an HIV protease inhibitor preferred for first-line treatment of patients in HIV treatment guidelines.

Background

• ATV is a substrate and inhibitor of CYP3A4 and is coadministered with RTV, a CYP3A4 inhibitor, to achieve high trough plasma concentrations.
• ATV-associated adverse effects include hyperbilirubinemia due to UGT1A1 inhibition and modest PR interval prolongation.
• GS-9350 may offer an alternative to RTV to boost ATV with the potential for reduced adverse biochemical effects.

Objectives

• To evaluate the pharmacokinetics of ATV when coadministered with GS-9350 or RTV.
• To evaluate the safety of administration of ATV in combination with GS-9350 or RTV.

Methods

Demographics

• 42 healthy subjects enrolled.
• 28 males, 14 females.
• Mean age: 28 yrs (range: 18 – 45).
• Ethnicity: 28 White, 10 Black, 3 Asian, 1 Native American.

Adisposition

• 33 completed study.
• 5 discontinuations.
• 2 withdrawal consent.
• 2 Investigator’s discretion.

Results

Plasma PK sampling performed over 24 hours; ATV, GS-9350, and ATV/r exposures were bioequivalent. Data expressed as arithmetic mean (%CV) or *median (Q1, Q3).

Plasma PK Parameters of ATV Following ATV/r 300/100 mg and ATV/GS-9350 300/100 mg Dosing

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Pharmacokinetics

• Bioequivalent ATV exposures between ATV/GS-9350 300/100 mg and ATV/r 300/100 mg.
• ATV/GS-9350 300/100 mg provided lower ATV exposures compared to ATV/r 300/100 mg.

Safety

• No Grade 3/4 AEs, serious AEs.
• Discontinuations due to AEs (moderate (Grade 2) severity).
• No changes in ALT, AST, GGT.

Conclusion

ATV/GS-9350 300/100 mg provides bioequivalent ATV exposures to ATV/r.

References