Impact of Mild, Moderate, and Severe Renal Impairment on Temsavir Pharmacokinetics Following Oral Administration of Fostemsavir on HIV-1 Infected Patients

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Introduction
Fostemsavir (FTR, previously called BMS-849869/GSK1349531A) is a first-in-class attachment inhibitor produg that is metabolised to its active moiety, temsavir (TMR) which binds to the viral envelope glycoprotein 120 (gp120), locking it in a conformational state that inhibits initial interaction between the virus and host immune cells. This prevents viral entry and attachment into the host CD4+ T-cells. FTR 600 mg BID is being evaluated in heavily treatment-experienced (HTX), HIV-1-infected participants.

The major route of TMR elimination is biotransformation with <2% as unchanged TMR in the urine.

Safety Results
Subjects (excluding those with ESRD on HD) received a single oral dose of FTR 600 mg extended-release (ER) tablet with a standard meal on Day 1.

Subjects with ESRD on HD received FTR 600 mg ER tablet with a standard meal after HD (Period 1; reference), and following an adequate washout, 4 hours before HD (Period 2; test).

Study Population
Inclusion criteria for subjects with normal renal function included age ≥18 and good health status as determined by medical history, PE, BMI 18.0-30.0 kg/m², ECG, vital signs, and clinical laboratory evaluations.

Subjects with renal impairment may have had clinical, ECG, and laboratory findings consistent with their disease status and good health status as determined by medical history, PE, BMI 18.0-30.0 kg/m², ECGs, and clinical laboratory determinations.

Pharmacokinetic Results
No dosage adjustment of FTR required response analysis.

Effect of HD on Pharmacokinetics
HD initiated 4 hours after TMR dosing was associated with a 11% reduction in total TMR AUC(0-T) in Crearies to TMR PK off HD. Categorical statistical analysis showed unchanged TMR AUC(INF), T or Crearies in 31%, higher AUC (90% CI 1.307 [0.859, 1.998], and 10% lower (0.899 [0.575, 1.403]), respectively, in subjects with ESRD after HD (Period 1; reference) compared with normal renal function.

Safety Results
There were no deaths during this study.

For subject (Group E) experienced 2 AEs (pneumonia and pulmonary edema), classified as serious and significant AEs, that resulted in discontinuation of the study. However, both AEs were considered unrelated to FTR.

Discussion
Model-predicted average increases in plasma TMR Cmax, fu and AUC(0-INf)fu were 15% and 46%, respectively, in subjects with mild, moderate, and severe RI in comparison to normal renal function.

Conclusions
As TMR is not readily cleared by HD, FTR may be administered to patients with ESRD without regard to time of HD.