Impact of Mild, Moderate, and Severe Renal Impairment and Hemodialysis on Temsavir Pharmacokinetics Following Oral Administration of Fostemsavir, an Attachment Inhibitor for Heavily Treatment Experienced HIV-1 Infected Patients

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Introduction

- Fostemsavir (FTR, previously called BMS-663068/GSK3684934) is a first-in-class attachment inhibitor prodrug that is metabolised to its active moiety, temsavir (TMR)[1] 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 attachment and entry into the host CD4+ T-cells.[2] FTR 600 mg BID is being evaluated in heavily treatment-experienced (HTE), HIV-1-infected participants.
- The major route of TMR elimination is biotransformation with <2% as unchanged TMR in the urine and feces. Renal impairment (RI) can lead to changes in hepatic/gut drug metabolism.
- This study 206217 (NCT02674581) assessed the impact of RI, a comorbidity in HTE patients, on TMR pharmacokinetics (PK) and safety following single dose administration given time-independent TMR PK.

Objectives

- To assess the effect of varying degrees of RI and the effect of HD on TMR PK following a single oral dose of FTR 600 mg.
- To assess the safety of TMR in subjects with normal renal function and subjects with impaired renal function following single dose administration.

Methods

- Study 206217 was an open-label, parallel-group study in HIV-seronegative adults with varying degrees of renal function with estimated glomerular filtration rate (eGFR) determined by MDRD formula.

Group	Population	eGFR (mL/min/1.73 m²)	Subjects/Group
A	Normal renal function	≥90	6
B	Mild renal function	60 to 89	6
C	Moderate renal function	30 to <60	6
D	Severe renal function	<30 not on HD	6
E	End-stage renal dysfunction	<30 on HD	6

- 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 18.0-32.0 kg/m², ECG, vital signs, and clinical laboratory evaluations.
- Subjects with renal impairment may have had clinical, ECG, and laboratory findings consistent with their degree of renal dysfunction, and good health status as determined by medical history, PE, BMI 18.0-38.0 kg/m², ECGs, and clinical laboratory determinations.

Pharmacokinetic Assessments and Statistics

- Serial blood samples were collected up to 96 hours post-dose; PK parameters were estimated by non-compartmental methods.
- Linear regression analysis of pooled data (excluding ESRD) was the primary analysis used to estimate the effect of RI on total and unbound TMR PK.
- The effect of HD on TMR PK was also assessed by comparing ESRD between before HD (Period 2, test) versus after HD (Period 2, reference) using ANOVA.

Safety Assessments

- Safety and tolerability endpoints including incidence of AEs, significant AEs, AEs leading to discontinuation, as well as marked abnormalities.

Results

Subject Demographics

- Thirty adults were dosed (6/group) and 29 completed the study (see Safety Results).
  - Mean age was 57.0, 66.3, 64.0, 60.0, 44.8 years in normal, mild, moderate, severe RI and ESRD, respectively.
  - Mean BMI balanced across the groups: 28.68, 27.83, 29.50, 27.07 and 26.38 kg/m² in normal, mild, moderate, severe RI and ESRD, respectively.
  - Majority were male: 50, 66.7, 50, 83.3, 66.7% in normal, mild, moderate, severe RI and ESRD, respectively.
  - Majority were white: 83.3, 83.3, 66.7, 66.7, 16.7% in normal, mild, moderate, severe RI and ESRD, respectively.

Pharmacokinetic Results

- All 30 subjects were included in PK analysis; TMR concentration-time profile is shown in Figure 1.
- No significant impact of renal function on TMR PK based on eGFR-based regression analysis (95% CI of all slope estimates contained unity); ≤2% change in total and 15% change in unbound TMR AUC(INF) or Cmax in subjects with RI, respectively (Figure 2). ANOVA analysis showed a 43% decrease in TMR renal clearance with severe RI compared to normal renal function.
- Mean unchanged TMR in urine across dose groups was ≤1%.
- Mean TMR unbound fraction highest for severe and ESRD RI: 12, 12, 13, 19, and 16% in normal, mild, moderate, severe RI and ESRD, respectively.

Effect of HD on Pharmacokinetics

- HD initiated 4 hours after TMR dosing was associated with an 11% reduction in total TMR AUC(INF) and 46% increase in Cmax relative to TMR PK off HD. Categorical statistical analysis showed unbound TMR AUC(INF)_fu and Cmax_fu were 31% higher (GMR [90% CI] 1.307 [0.859, 1.988]) 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.
- One 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.
- 10 subjects (33.3%) reported 31 AEs; incidence of treatment-emergent AEs did not appear to increase with increasing severity of renal impairment.
- As expected, subjects with varying renal impairment had clinical laboratory results (eg, red blood cell indices, electrolytes, blood urea nitrogen, and protein) consistent with degree of renal dysfunction; however, no marked laboratory abnormalities were reported as an AE; no abnormalities in ECG, vital signs, or PEs reported as an AE.

Figure 1. Mean + SD Total TMR Plasma Concentration-Time Profiles by Renal Function Following Single Dose FTR 600 mg

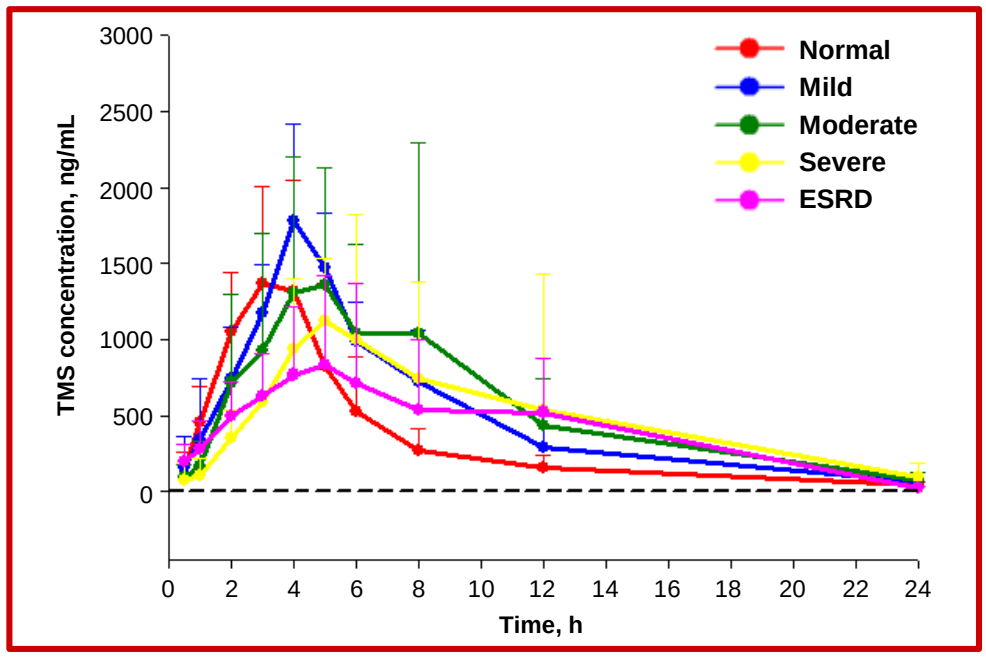
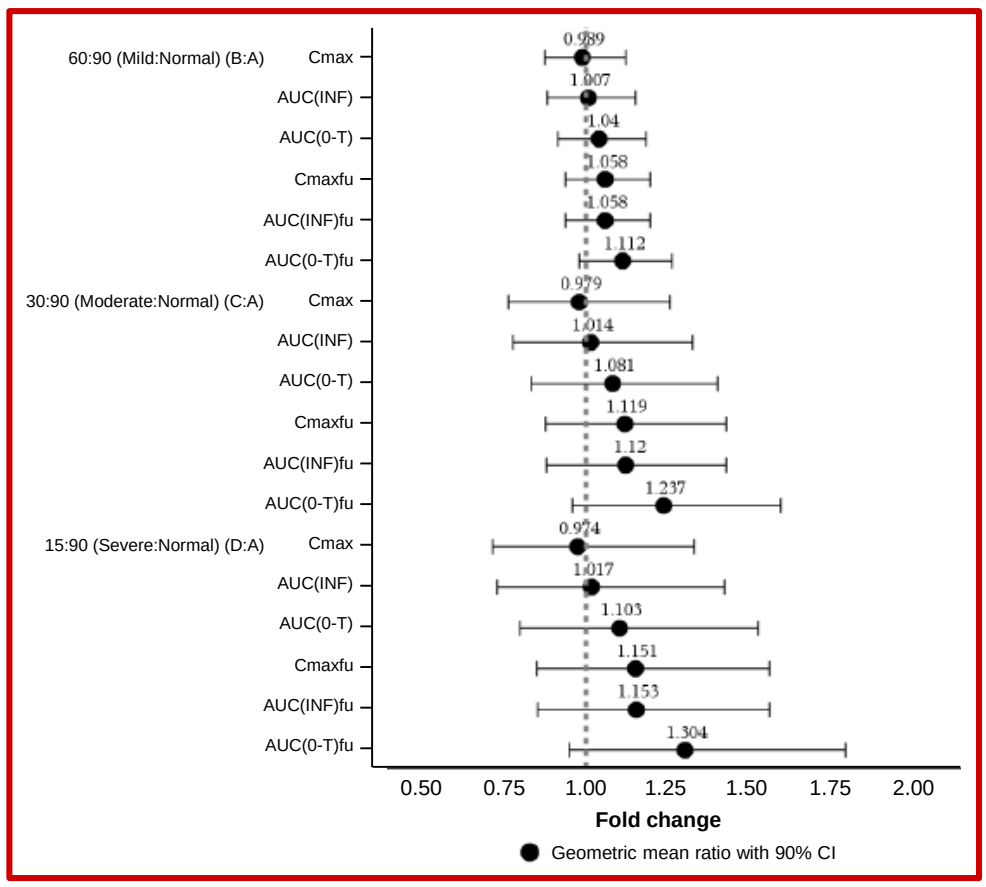


Figure 2. Forest Plot of Effects of Renal Impairment on Total and Unbound TMR PK Based on eGFR Regression Analysis



Discussion

- Model-predicted average increases in plasma TMR Cmax_fu and AUCinf_fu were ≤15% and AUClast_fu was ≤30% for mild, moderate, and severe RI. No dosage adjustment of FTR required with RI because the upper bounds of the 90% CIs on TMR Cmax and Cmax_fu are lower than the upper no effect boundary established based on TMR exposure-response analysis.
- ESRD had less impact on total and unbound TMR PK than mild, moderate, or severe RI; may be because routine HD eliminates endogenous compounds that displace TMR from protein binding sites and/or impact on TMR transport or metabolism. HD had a minimal impact on TMR total and unbound PK; TMR was not readily cleared by HD approximately 12% of dose removed during a 4-hour HD.
- There was no trend in AE incidence with worsening renal function and no new safety signal identified.

Conclusions

- FTR 600 mg tablet twice daily can be administered without dose adjustment in patients with mild, moderate and severe renal impairment and with ESRD.
- As TMR is not readily cleared by HD, FTR may be administered to patients with ESRD without regard to time of HD.

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References: 1. Brown J, et al. *J Pharm Sci.* 2013;102(6):1742–1751. **2.** Langley DR, et al. *Proteins*. 2015;83:331–350.

Disclosure: Heather Sevinsky was employed by ViiV Healthcare at the time of study reporting; now an employee of Arbutus Biopharma.