Poster Number

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Bioequivalence of Two Pediatric Formulations Vs Adult Tablet Formulation of Elvitegravir

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Introduction

- Safe and effective pediatric antiretroviral (ARV) therapeutic options are needed
  - Perinatally infected children require life-long ARV therapy
  - There is a need for convenient, well-tolerated pediatric therapies with activity against HIV resistant to existing classes
  - No once-daily integrase inhibitor is approved for use in HIV-infected children younger than 12 years
- Elvitegravir (EVG) is a once-daily integrase inhibitor in development as a single agent for the treatment of adults and children with HIV-1 infection
  - In regulatory review in the United States
  - Approved in the European Union for treatment of adults when coadministered as part of an antiretroviral regimen containing a boosted protease inhibitor
- EVG has also been coformulated with cobicistat (COBI), emtricitabine (FTC), and tenofovir DF (TDF) into the single tablet regimen E/C/F/TDF (Stribild; STB) approved for the treatment of HIV-1 infection in adults
- EVG pharmacokinetics (PK) well characterized and previous taste assessment of an EVG oral suspension demonstrated that flavors are unlikely to be patient-perceptible due to the lack of chalky, oily, drying, or tongue stinging in the formulation

Objectives

Primary:

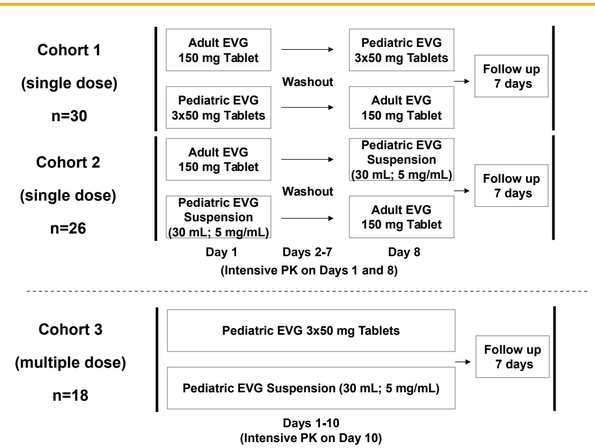
- Evaluate the bioequivalence of the age-appropriate EVG pediatric tablet and suspension formulations compared with the adult EVG tablets in healthy adult subjects

Secondary:

- Evaluate the safety of the age-appropriate EVG pediatric tablet and suspension formulations and adult EVG tablets in healthy adult subjects

Methods

Figure 1. Study Design



Methods

- All EVG treatments across all cohorts included 100 mg of RTV as a pharmacoenhancer (EVG/r)
- On PK days, study treatments were administered in the morning following an overnight fast and within five minutes of the completion of a standardized meal
- Intensive PK sampling performed over 48 hours
  - EVG PK determined using validated LC/MS/MS assays
- PK parameters estimated using non-compartmental methods and WinNonlin® software v6.3 (Pharsight Corporation, Mountain View, CA, USA)
- A parametric (normal theory) analysis of variance (ANOVA) using a mixed effects model was fitted to the natural logarithmic transformation of PK parameters of each analyte
- Bioequivalence (BE) 90% confidence interval (CI) (pediatric formulation: adult tablet) about geometric mean ratio (GMR) as follows: EVG AUC_{inf}, AUC_{last}, and C_{max}: 80% to 125%
  - Cohorts 1 and 2 contained >85% power to conclude BE
  - In Cohort 3, only descriptive PK was assessed

Table 1. Demographics

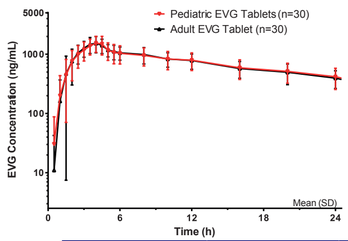
	Cohort 1	Cohort 2	Cohort 3
Subjects	30 enrolled/ completed	26 enrolled/ completed	18 enrolled/ completed
Sex	19 males 11 females	15 males 11 females	10 males 8 females
Age (mean [range])	28 (20-44) yrs	27 (20-40) yrs	27 (18-41) yrs
Weight (mean [range])	74.5 (56.0–109) kg	72.9 (55.4–99.8) kg	74.6 (52.7–102) kg
Race	10 White 18 Black 2 Asian	10 White 16 Black	7 White 10 Black 1 American Indian

Results

Safety

- All enrolled subjects across all cohorts (n=74) completed the study
- Study treatments generally well tolerated
- No discontinuations due to adverse events (AEs)
- No Grade 2, 3, 4 or serious AEs
- No Grade 3, 4 laboratory abnormalities except for two female subjects that experienced Grade 3 hematuria

Figure 2. Cohort 1: Pharmacokinetics of Pediatric Tablet

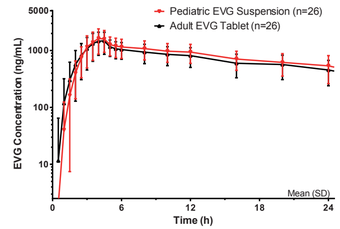


EVG pediatric tablets are BE compared to adult EVG tablet

PK Parameter mean (%CV)	Pediatric EVG 3x50 mg Tablets	Adult EVG 150 mg Tablet	GMR % (90% CI)
AUC_{inf} (ng*h/mL)	22200 (34)	22100 (36)	100 (93.8, 107)
AUC_{last} (ng*h/mL)	21100 (32)	21000 (29)	99.6 (93.2, 106)
C_{max} (ng/mL)	1650 (30)	1640 (28)	100 (93.1, 107)

Results (cont'd)

Figure 3. Cohort 2: Pharmacokinetics of Pediatric Suspension



EVG pediatric suspension is BE compared to adult EVG tablet

PK Parameter mean (%CV)	Pediatric EVG pediatric suspension (30 mL; 5 mg/mL)	Adult EVG 150 mg Tablet	GMR % (90% CI)
AUC_{inf} (ng*h/mL)	25000 (36)	22800 (36)	109 (102, 118)
AUC_{last} (ng*h/mL)	24200 (36)	21800 (37)	111 (103, 120)
C_{max} (ng/mL)	1800 (40)	1650 (38)	108 (98.7, 118)

Table 2. Cohort 3: Steady State PK of Pediatric Tablet and Suspension

PK Parameter mean (%CV)	Pediatric EVG 3x50 mg Tablets (n=9)	Pediatric EVG pediatric suspension (30 mL; 5 mg/mL) (n=9)
AUC_{tau} (ng*h/mL)	24100 (16)	20600 (24)
C_{max} (ng/mL)	2470 (23)	1940 (30)
C_{tau} (ng/mL)	411 (18)	377 (31)

- **EVG steady state PK comparable between pediatric tablet and suspension formulations**
- **Results consistent with historical data of boosted EVG, including achievement of mean trough concentrations (EVG C_{tau}) ~9.2 and 8.5-fold, respectively, above the IC_{95} (44.5 ng/mL)**

Conclusions

- **EVG pediatric tablet and suspension formulations were each bioequivalent to adult tablets, when coadministered with RTV**
- **Steady state PK of both pediatric formulations were consistent with historical data of boosted EVG**
- **EVG pediatric formulations were well tolerated and overall safety profile consistent with previous studies with EVG adult tablets**
- **These study findings support evaluation of these pediatric formulations in HIV infected children in an ongoing Phase 2/3 study**