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Pharmacokinetics and Preliminary Safety of Elvitegravir in HIV-1 Infected Pediatric Subjects

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Introduction

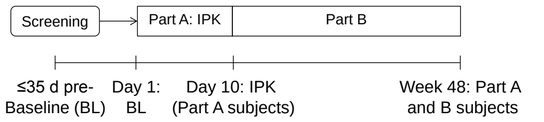
- Safe and effective pediatric antiretroviral therapeutic options are needed, particularly in treatment-experienced patients and those below age 12
- Elvitegravir 150 mg (EVG, E) is an approved once-daily integrase inhibitor for treatment of HIV-1 infection in adults as part of the single-tablet regimen (STR) Stribild containing cobicistat (COBI, C), emtricitabine (F), and Tenofovir DF (TDF)[a] or when co-administered with a ritonavir (r)-boosted protease inhibitor (PI/r)[b]
  - EVG 85 mg is used in combination with ATV/r or LPV/r due to increased EVG plasma concentrations via inhibition of UGT enzymes
- EVG has also been co-formulated with Tenofovir Alafenamide (TAF) in the E/C/F/TAF STR, which is currently under regulatory review in the United States and European Union
- Previous studies have confirmed use of the adult dose of ritonavir- or COBI-boosted EVG in adolescents (12 to <18 year olds)[c,d,e]
- Study GS-US-183-0160 is an ongoing, Phase 2/3, open-label, multi-cohort study evaluating the safety and pharmacokinetics (PK) of EVG in HIV-1 infected, anti-retroviral treatment-experienced pediatric subjects
- This presentation comprises the PK and preliminary safety data from the Part A lead-in phase of Cohort 2 (6 to < 12 year olds)

Objectives

- Evaluate the steady state PK, tolerability, and preliminary safety and confirm the dose of EVG when co-administered with a PI/r in HIV-1 infected antiretroviral treatment-experienced subjects 4 weeks to <18 years of age

Methods

Figure 1. Study design: 6 to < 12 year old Cohort (Dose Confirmation in Part A)



* Suppressed subjects to only participate in Part A of the study. These subjects would discontinue EVG and complete the study following the Day 10 intensive PK visit.

- Key eligibility criteria
  - Either suppressed (HIV-1 RNA of <50 copies/mL at screening) OR failing (HIV-1 RNA >1000 copies/mL) with at least 1 resistance mutation
  - Fully sensitive to EVG
  - No prior treatment with an INSTI
- EVG co-administered with a background regimen, which could include a PI/r (e.g., ATV/r, LPV/r, DRV/r, fAMP/r or TPV/r)
- Study conducted with age de-escalation design; cohorts with older children precede cohorts with younger children
  - Intensive PK (IPK) sampling performed on or after Day 10 (steady state) to support EVG dose confirmation in Part A lead-in phase; Target N=12
  - Confirmation of EVG dose in Part A supports continuation into Part B of that Cohort (longer term follow-up) and initiation of dosing in the subsequent Cohort (lower age group)
- EVG exposure achieved in pediatric subjects compared to historical data

Results

Table 1. Demographics

	Part A, Cohort 2: Age 6 to < 12 Years Old		
	Screening HIV-1 RNA < 50 c/mL (n=14)	Screening HIV-1 RNA > 1000 c/mL (n=2)	Total (n=16)
Mean CD4 cells/µL, Mean (SD)	811 (303)	527 (72.8)	
Sex (male/female), n	8/6	2/0	10/6
Median age, y (range)	10 (6, 11)	8 (7,9)	9 (6,11)
Median weight, kg (range)	25.7 (18.0, 46.8)	33.8 (19.5, 48.0)	25.7 (18.0, 48.0)
Median BSA, m² (range)	0.97 (0.75, 1.44)	1.04 (0.78, 1.30)	0.97 (0.75, 1.44)
Background Regimen/ EVG Dose (n)	ATV/r/85 mg EVG (n=1)		
	LPV/r/85 mg EVG (n=4)	LPV/r/85 mg EVG (n=1)	
	LPV/r/50 mg EVG (n=9)	LPV/r/50 mg EVG (n=1)	
Race	2 Asian, 10 Black, 2 White	1 Asian, 1 Black	3 Asian, 11 Black, 2 White

Results (cont'd)

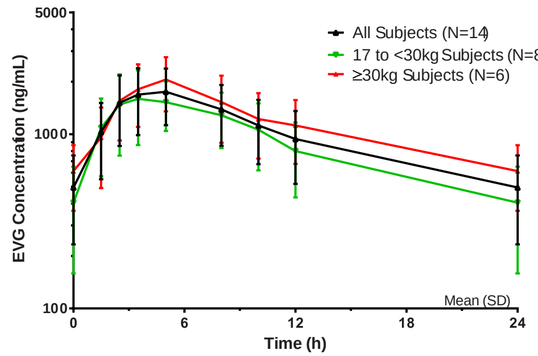
Disposition

- 16 subjects enrolled into Cohort 2 Part A: 14 suppressed, 2 failing
- Complete PK data available for 14 subjects (unavailable for 2 suppressed subjects)
  - 1 discontinued before Day 10 IPK (withdrew consent)
  - 1 replacement subject PK data not analyzed

Safety and Efficacy

- No deaths or AEs leading to discontinuation
- Majority of AEs were mild to moderate and unrelated to EVG
- All suppressed subjects remained suppressed through 30 day follow-up after Day 10
- Two failing subjects achieved virologic suppression HIV-1 RNA <100 copies/mL by Week 12 (followed for up to 20 weeks)

Figure 2. EVG Pharmacokinetics



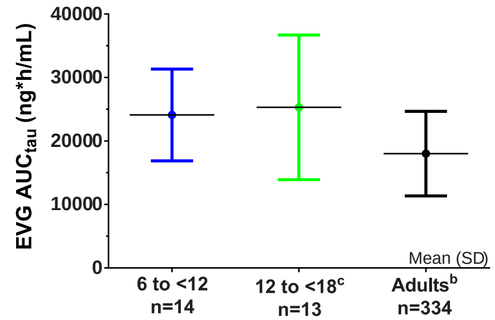
- Fourteen subjects completed the IPK assessment in Part A of Cohort 2
- EVG doses were based on co-administered PI/r and weight:
  - N=13 were on LPV/r and N=1 on ATV/r
  - N=6 received adult dose: 85 mg EVG (≥30 kg)
  - N=8 received reduced dose: 50 mg EVG (≥17 to <30 kg)

Table 2. EVG Pharmacokinetics and Statistical Comparisons

EVG PK Parameter Mean (%CV)	EVG + PI/r Pediatric Subjects (Test) Mean (%CV)	EVG + PI/r Adults (Reference; n=334) Mean (%CV)	GMR (%) (90% CI)*
EVG Dose (50 & 85 mg): All Subjects (N=14)			
AUC_{tau} (ng*h/mL)	24100 (30)	18000 (37)	136 (117, 159)
C_{max} (ng/mL)	2020 (30)	1380 (28)	147 (127, 169)
C_{trough} (ng/mL)	494 (53)	378 (57)	129 (96.1, 174)
EVG Dose (85 mg): Subjects ≥ 30 kg (N=6)			
AUC_{tau} (ng*h/mL)	27400 (21)	18000 (37)	159 (131, 192)
C_{max} (ng/mL)	2200 (27)	1380 (28)	160 (125, 205)
C_{trough} (ng/mL)	614 (41)	378 (57)	175 (123, 248)
EVG Dose (50 mg): Subjects ≥ 17 kg to < 30 kg (N=8)			
AUC_{tau} (ng*h/mL)	21600 (36)	18000 (37)	121 (96.2, 153)
C_{max} (ng/mL)	1890 (32)	1380 (28)	137 (113, 167)
C_{trough} (ng/mL)	405 (61)	378 (57)	103 (65.7, 162)

*GMR (90% CI): Geometric Mean Ratio (90% Confidence Interval)

Figure 3. EVG Exposure by Age Group



EVG Pharmacokinetic Summary

- EVG doses, when co-administered with a PI/r in 6 to <12 year old subjects, result in comparable exposures across weight bands
- Mean EVG C_{trough} was ~11-fold above the *in vitro* protein-binding adjusted IC_{95} (44.5 ng/mL); all subjects' C_{trough} were above the IC_{95}
- Study data are consistent with the range of EVG exposures observed in children 12 to <18 years of age when co-administered with a PI/r (Mean (%CV) AUC_{tau}: 25300 (45) hr*ng/mL, C_{max}: 2140 (45) ng/mL, C_{trough}: 627 (69) ng/mL)[c] and are comparable to exposures associated with safety and efficacy in adults
- Regression analyses showed no statistically significant trends in EVG PK parameters with age, sex, weight, BMI, or BSA (data not shown)

Conclusions

- **Administration of EVG once daily with a PI/r in children 6 to <12 years old provides therapeutic EVG exposure, with mean trough concentrations ~11-fold above the protein-binding adjusted IC_{95} (44.5 ng/mL)**
- **Based on limited data in a small number of subjects, EVG appears safe and well-tolerated**
- **These results support continued evaluation of the efficacy and safety of EVG in pediatric populations**

References

a. Stribild™ US Prescribing Information
b. Vitekta™ US Prescribing Information
c. Study GS-US-183-0152: Gaur A, et al, CROI 2010
d. Study GS-US-236-0112: Gaur A, et al, CROI 2014
e. Study GS-US-292-0106: Kizito H, et al, CROI 2015