

Introduction

- Elvitegravir (EVG) is a potent HIV-1 integrase inhibitor in development for the treatment of HIV-infected patients
- Once-daily boosted-EVG in adults provides high trough concentrations and low inter- and intra-subject variability¹
- EVG/r has demonstrated durable antiviral efficacy and has been well tolerated in antiretroviral (ARV) treatment-experienced adults when dosed with other active ARVs^{2,3}

Background

- The availability of novel, efficacious, and well tolerated ARVs with convenient dosing regimens is an unmet medical need for treatment-experienced HIV-1 infected adolescents
- Study GS-US-183-0152 is a prospective, open-label, multi-center, non-randomized, dose-confirmation study of EVG plus a background regimen (BR) containing a boosted-protease inhibitor (PI) in treatment-experienced HIV-1 infected adolescents

Objectives

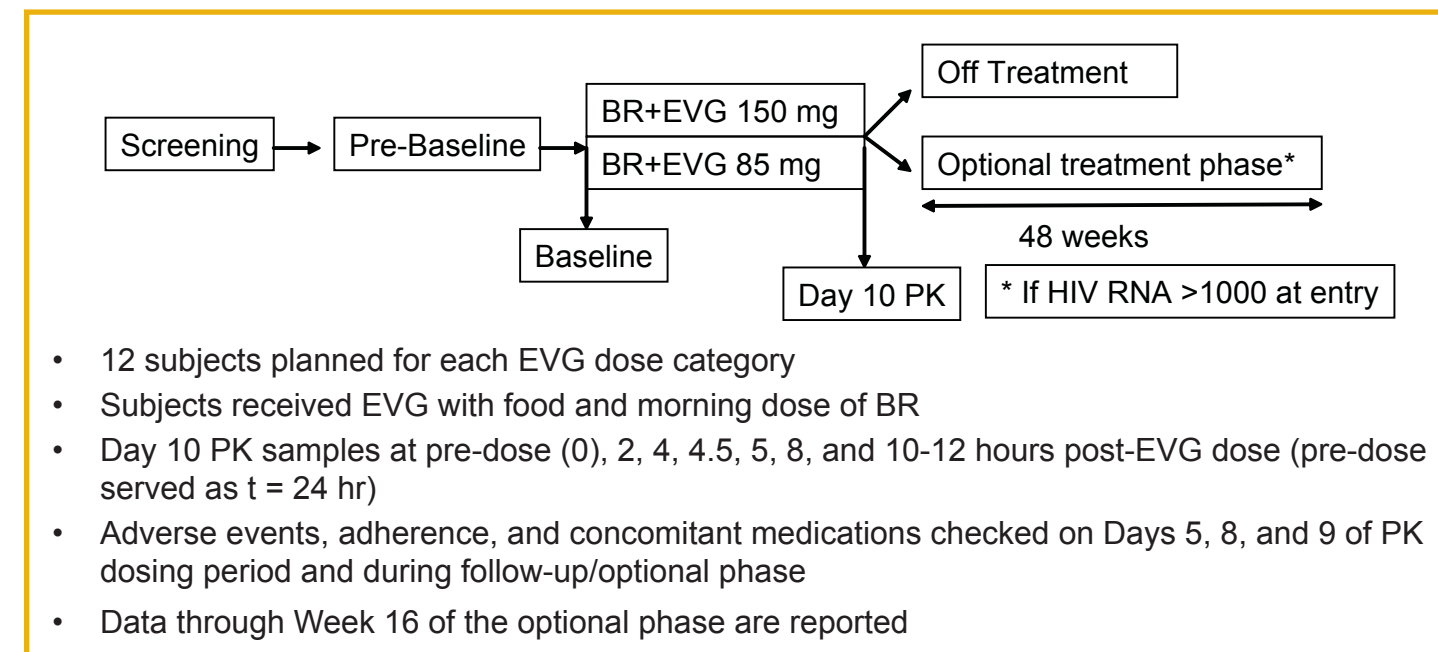
- To evaluate the pharmacokinetics (PK) and confirm the doses of EVG in HIV-1 infected ARV treatment-experienced adolescent patients
- To evaluate the safety and tolerability of boosted-EVG in HIV-1 infected ARV treatment-experienced adolescent patients

Methods

- Key Eligibility Criteria
 - 12 to <18 years of age
 - Body surface area ≥ 1.2 m²
 - Weight ≥ 40 kg
 - HIV RNA >1000 copies/ml or <400 copies/ml
 - No prior experience with an HIV integrase inhibitor
- BR
 - Existing regimen with PI/r if screening HIV RNA <400 copies/ml
 - New regimen (at least 2 fully-active ARVs, including PI/r) if HIV RNA >1000 copies/ml
- RTV-boosted protease inhibitor (PI/r) always part of BR
 - EVG 150 mg: Darunavir/r, tipranavir/r, or fosamprenavir/r
 - EVG 85 mg: atazanavir/r or lopinavir/r

Methods (cont'd)

Figure 1. Study Design



Results

Table 1. Baseline Characteristics

Characteristic	EVG 85 mg + BR (n=14)	EVG 150 mg + BR (n=11)
Age, years (range)	15 ± 1.8 (12-17)	16 ± 1.0 (14-17)
Male	7	6
Female	7	5
White	3	4
Black	11	7
HIV RNA Log ₁₀ copies/ml	2.4 ± 1.2	3.6 ± 0.83
<400 copies/ml	10	2
>1000 copies/ml	4	9
CD4 cells/μl	528 ± 232	406 ± 277
Weight (kg)	60 ± 13	65 ± 20
BSA (m ²)	1.6 ± 0.2	1.7 ± 0.3
Years on ARV	4.6 ± 3.5	3.8 ± 3.4

Data shown as mean ± SD
BR PI/r (n): darunavir (9), atazanavir (6), fosamprenavir (2) and lopinavir (8); 24 of 25 patients received ≥ 1 NRTI

Disposition and Safety

- PK evaluation completed by 23 of 25 patients
 - Two discontinuations
 - 1 due to AEs including Grade 3 vomiting and chills
 - 1 due to AEs including Grade 3 nausea, vomiting, chills and dizziness
- Most AEs mild-moderate; common treatment-emergent AEs (n) in 25 patients dosed:
 - Gastrointestinal (14) and neurologic (10)
- No Grade 4 AEs or study drug-related SAEs
- Treatment-emergent laboratory abnormalities (n)
 - Mostly Grade 1 (10) or Grade 2 (6)
 - Grade 3: platelets (1), total bilirubin (1), blood in urine (1)
 - Grade 4: creatinine kinase (1)
- Nine patients entered optional 48-week phase

Results (cont'd)

Pharmacokinetics

Figure 2. Elvitegravir (EVG) Plasma Concentration-Time Profile

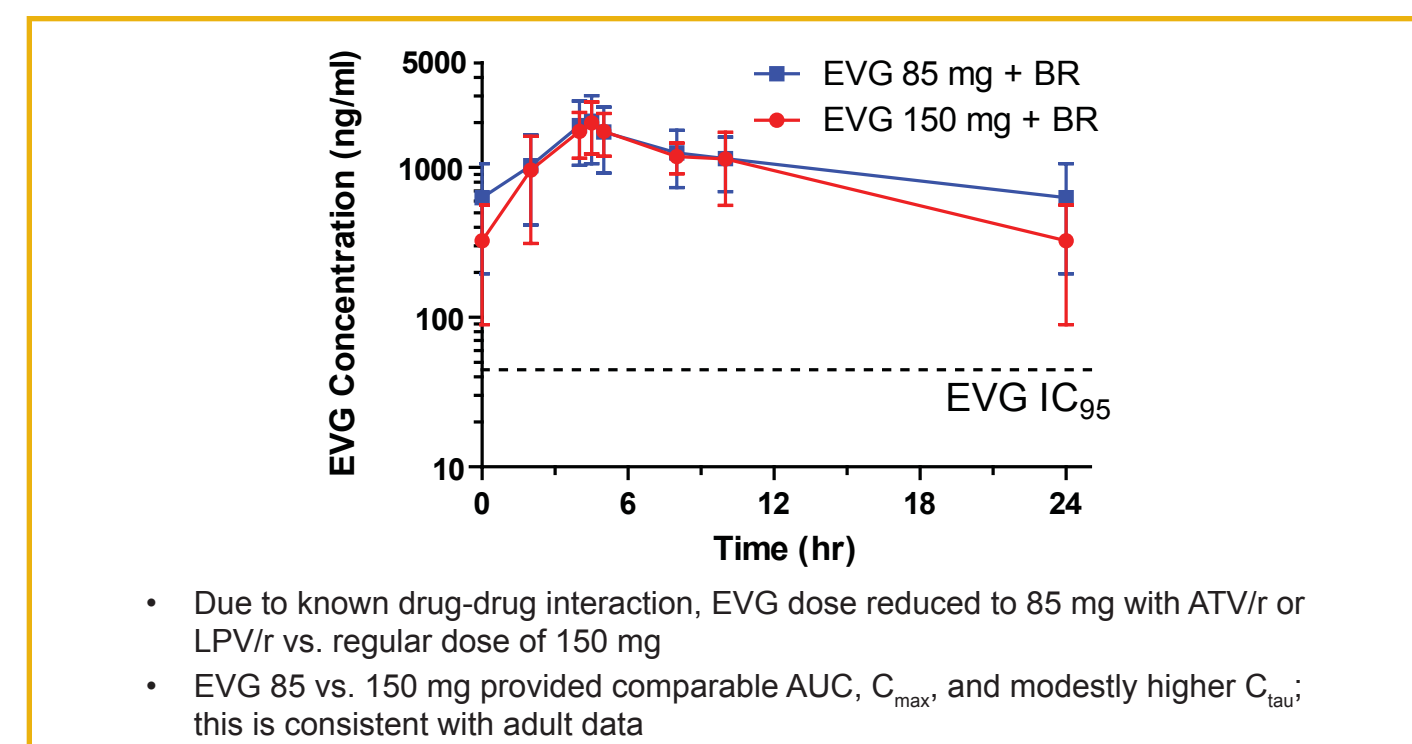


Table 2. Plasma Pharmacokinetic Parameters of Once-daily Boosted EVG

EVG PK	HIV-1 Infected Adolescent Patients ^a	
	EVG 85 mg (n = 13)	EVG 150 mg (n = 10)
AUC _{tau} (ng·h/mL)	25300 (45%)	21200 (36%)
C _{max} (ng/mL)	2140 (45%)	2070 (36%)
C _{tau} (ng/mL)	627 (69%)	325 (73%)
T _{1/2} (h)*	15.1 (11.1, 19.1)	7.6 (5.7, 13.5)
T _{max} (h)*	4.5 (4.3, 4.7)	4.5 (4.0, 4.5)

a. Data shown as arithmetic mean (%CV) or *median (Q1,Q3);
Adult healthy subject (n=42) mean EVG AUC_{tau} 22,200 ng.h/ml, C_{tau} 471 ng/ml; Adult HIV patient (intensive PK substudy (n=12) of Phase 2 study^{2,3}) mean EVG AUC_{tau} 17,000 ng.h/ml, C_{tau} 260 ng/ml

- EVG 150 mg exposures comparable between HIV-1 infected adolescent patients and adults
- Comparable AUC_{tau} and C_{max}, but higher C_{trough} between EVG 85 mg vs. EVG 150 mg, consistent with known interaction data in adults with ATV/r and LPV/r
- EVG mean C_{trough} 7-fold to 13-fold above IC₉₅ (protein-binding adjusted)

Efficacy

- Patients with >1000 copies/ml HIV-1 RNA entering optional 48-week treatment phase (n=9)
 - Median change from baseline in HIV-1 RNA:
 - -2.02 log₁₀ copies/ml by Week 2, -2.35 log₁₀ copies/ml by Week 16
 - Patients <400 copies/ml: 7 of 9 through Week 16 (6 <50 copies/ml)
 - Median change in CD4 cells: +160 cells/μl through Week 16

Conclusions

- In adolescent patients (12 to <18 years), EVG once-daily, when added to a PI/r BR, was well tolerated and provided plasma exposures comparable to those in HIV-infected adults
- These data support long term safety and efficacy evaluation of EVG in this pediatric population

References

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