Poster Number

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Bioequivalence of Two Pediatric Formulations Vs Adult Tablet Formulation of Cobicistat

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Introduction

- Alternate antiretroviral (ARV) pharmacoenhancers are needed for pediatric use due to the poor palatability of the ritonavir pediatric formulation
  - Boosted protease inhibitors (PIs) are recommended for treatment in HIV-infected pediatric populations, requiring life-long ARV therapy
  - Ritonavir is currently the only approved pharmacoenhancer for use with PIs in HIV-infected infants, children, and adolescents
  - In addition to palatability, metabolic adverse events and tolerability limit ritonavir use in some pediatric patients[1]
- Cobicistat (COBI), a pharmacoenhancer, is a mechanism-based CYP3A inhibitor devoid of antiretroviral activity
  - Approved in adults as a once-daily pharmacoenhancer of atazanavir 300 mg or darunavir 800 mg in the European Union
  - Approved in adults as a pharmacoenhancer in the once-daily single table regimen elvitegravir/COBI/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF; Stribild™; STB)

Objectives

Primary:

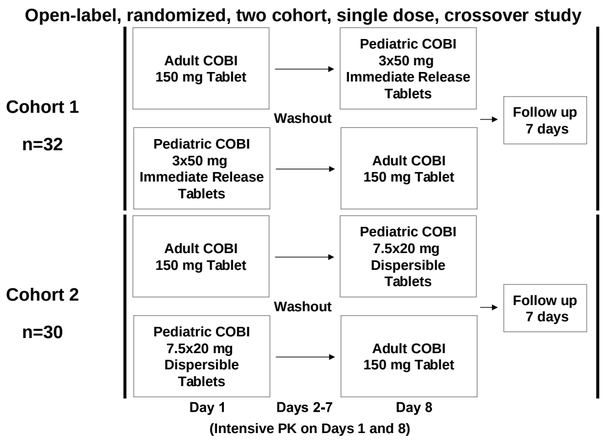
- Evaluate the bioequivalence of the age-appropriate COBI pediatric immediate release or dispersible tablet formulations compared with the adult COBI tablets in healthy adult subjects

Secondary:

- Evaluate the safety of the age-appropriate COBI pediatric immediate release or dispersible tablet formulations and adult COBI tablets in healthy adult subjects

Methods

Figure 1. Study Design



Methods

- Study treatments were administered in the morning following an overnight fast and within five minutes of the completion of a standardized meal
  - Dispersible tablet formulation administered as a suspension
- Palatability was assessed by a 7-point scale questionnaire taken by subjects within 1 hour of dosing
  - Scale: (1) dislike very much; (2) dislike moderately; (3) dislike slightly; (4) neither dislike or like; (5) like slightly; (6) like moderately; (7) like very much
- Intensive PK sampling performed over 48 hours
  - COBI 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:
  - COBI AUC_{inf}, AUC_{last}, and C_{max}: 80% to 125%
  - Cohorts 1 and 2 contained >90% power to conclude BE

Table 1. Demographics

	Cohort 1	Cohort 2
Subjects	32 enrolled 31 completed	30 enrolled 30 completed
Sex	19 males, 13 females	22 males, 8 females
Age (mean [range])	28 (19-45) yrs	29 (20-43) yrs
Weight (mean [range])	77.7 (56.2–103) kg	75.1 (55.5–92.1) kg
Race	9 White, 23 Black	14 White, 14 Black, 2 Asian

Results

Safety

- Study treatments generally well tolerated
- No discontinuations due to adverse events (AEs) and one subject withdrew consent
- No Grade 2, 3, 4 or serious AEs except for one subject that experienced Grade 2 gastrointestintal disorder while receiving the pediatric COBI immediate release tablet
- Renal function laboratory parameters were within normal range for all subjects
  - No clinically relevant changes in median serum creatinine, eGFR, or phosphate

Palatability

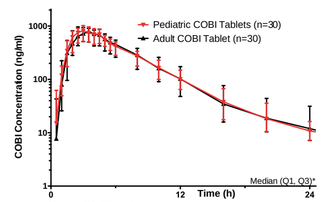
- All formulations were considered palatable by the majority of subjects
- For the immediate release tablet, most subjects indicated that they either “like very much” or “neither dislike or like”
- For the suspension, the overall rating was “neither dislike or like”

Palatability Rating	Adult COBI 150 mg Tablet (n=62)	Pediatric COBI 3x50 mg Immediate Release Tablets (n=31)	Pediatric COBI 7.5x20 mg Dispersible Tablets (n=30)
Mean (SD)	5 (1.5)	6 (1.6)	4 (1.5)

Scale: (1) dislike very much; (2) dislike moderately; (3) dislike slightly; (4) neither dislike or like; (5) like slightly; (6) like moderately; (7) like very much

Results (cont’d)

Figure 2. Cohort 1: Pharmacokinetics of Pediatric Immediate Release Tablets

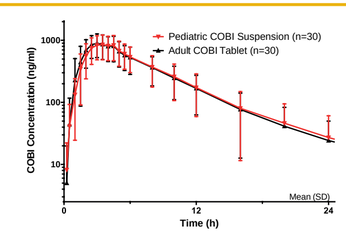


* Median (Q1, Q3) plotted due to an outlier subject with unusually high COBI concentrations in the reference arm

COBI pediatric immediate release tablets are BE compared to adult COBI tablet

PK Parameter mean (%CV)	Pediatric COBI 3x50 mg Tablets	Adult COBI 150 mg Tablet	GMR % (90% CI)
AUC_{inf} (ng*h/mL)	4950 (43)	5360 (53)	95.0 (88.9, 101)
AUC_{last} (ng*h/mL)	4910 (44)	5310 (53)	95.0 (88.9, 101)
C_{max} (ng/mL)	857 (35)	848 (33)	100 (92.8, 108)

Figure 3. Cohort 2: Pharmacokinetics of Pediatric Dispersible Tablets as Suspension



COBI pediatric dispersible tablets as suspension is BE compared to adult COBI tablet

PK Parameter mean (%CV)	Pediatric COBI pediatric suspension (7.5 tablets per dose)	Adult COBI 150 mg Tablet	GMR % (90% CI)
AUC_{inf} (ng*h/mL)	6260 (52)	6350 (46)	96.6 (90.1, 104)
AUC_{last} (ng*h/mL)	6220 (52)	6310 (47)	96.6 (90.0, 104)
C_{max} (ng/mL)	922 (40)	988 (36)	91.9 (86.8, 97.4)

Conclusions

- **COBI pediatric formulations, administered either as 50 mg immediate release tablets or as 20 mg dispersible tablets, were each bioequivalent to the COBI adult tablet formulation**
- **COBI pediatric formulations were considered palatable**
- **COBI pediatric formulations were well tolerated and overall safety profile consistent with previous studies with COBI adult tablets**
- **These study findings support evaluation of these pediatric formulations in HIV infected children in an ongoing Phase 2/3 study**

References

1. http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf

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