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Six-Month Outcome of F/TAF Cobicistat-Boosted Darunavir in Children 14 to < 25 kg

Poster 829

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Introduction

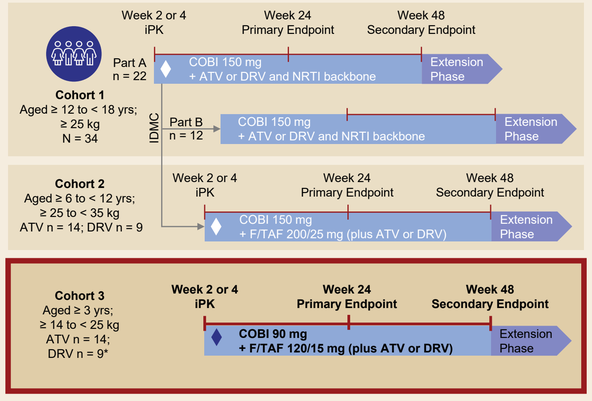
- F/TAF is a co-formulated once-daily tablet and is a guideline-recommended dual NRTI in children ≥ 14 kg when used with an INSTI or NNRTI[1]
- Although current WHO guidelines recommend an INSTI-based regimen with NRTI backbone as a first-line treatment in children and adolescents, some individuals can experience INSTI-associated toxicity, drug resistance and, ultimately, treatment failure[2,3]
- The PI DRV is recommended as an alternative second-line treatment in children and infants aged ≥ 3 years, and COBI is a PK enhancer with no antiviral activity that can be easily co-formulated with antiretroviral therapy[1,4]
- There are limited data on the PKs, safety and efficacy of COBI-boosted PIs in the pediatric population, including F/TAF with boosted PIs in young children
- GS-US-216-0128 is a multicenter, open-label, multicohort Phase 2/3 study evaluating the PKs, safety and efficacy of F/TAF plus ATV or DRV boosted with COBI (ATV/c and DRV/c, respectively) in virologically suppressed pediatric participants with HIV (NCT02016924)

Objectives

- This is an interim analysis to evaluate the PKs, safety and efficacy of F/TAF plus DRV/c in virologically suppressed children aged ≥ 3 years and weighing 14 to < 25 kg from Cohort 3 of study GS-US-216-0128

Methods

Figure 1. Study Design



*Enrollment: South Africa (n = 2) and Zimbabwe (n = 7)

Study Assessments

- **Efficacy (virologic and immunologic) outcomes**: Plasma HIV-1 RNA and relative/absolute CD4 cell count
- **PK outcomes**: iPK samples to examine steady-state exposures of DRV, COBI, FTC, TAF and TFV, including AUC_{tau}, C_{max} and C_{tau}
- **Safety and tolerability outcomes**: AEs and clinical laboratory assessment, including chemistry and hematologic profiles

Results

Table 1. Baseline Demographics and Disease Characteristics

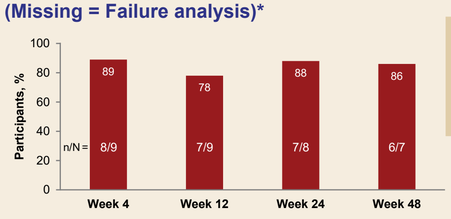
	Cohort 3: F/TAF + DRV/c (N = 9)
Median age, years (Q1, Q3)	4 (3, 6)
Female, n (%)	5 (56)
Median weight, kg (Q1, Q3)	16 (16, 17)
Median weight, Z-scores (Q1, Q3)	-0.4 (-1.7, +0.1)
Median height, Z-scores (Q1, Q3)	-0.8 (-1.7, +0.3)
Race, n (%)	
Black	2 (22)
Other	7 (78)
Hispanic or Latinx ethnicity, n (%)	0
HIV-1 RNA < 50 c/mL, n (%)	9 (100)
Median CD4 count, cells/μL (Q1, Q3)	1,237 (844, 1,490)
Median CD4, % (Q1, Q3)	41 (35, 42)
Vertical transmission, n (%)	9 (100)
Median $eGFR_{Schwartz}$, mL/min/1.73 m^2 (Q1, Q3)	166 (144, 169)
Baseline third agent, n (%)	
LPV/r	7 (78)
EFV	2 (22)

Duration of Exposure

- Median (Q1, Q3) duration of exposure: 66 weeks (63, 72), N = 9

Efficacy Outcomes

Figure 2. Virologic: HIV-1 RNA < 50 c/mL (Missing = Failure analysis)*



Viral suppression was 100% at all visits for participants with data available for virologic analysis

*Treatment failures at visits were due to missing data

Figure 3. Immunologic: Change From Baseline in Absolute CD4 Cell Count

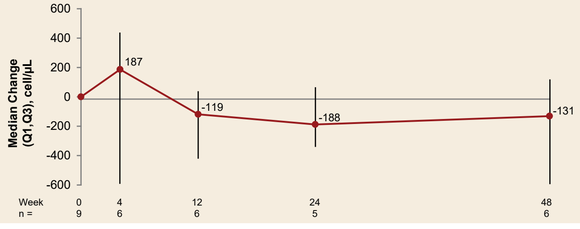
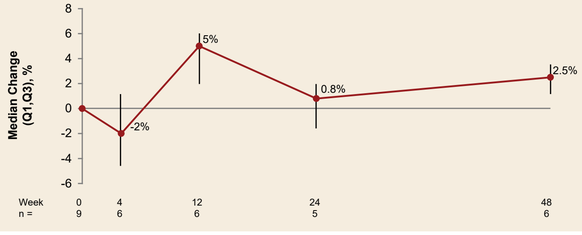


Figure 4. Immunologic: Change From Baseline in Relative CD4



Pharmacokinetic Outcomes

Table 2. Mean Exposures

	DRV (n = 9)	COBI (n = 8)	FTC (n = 8)	TAF (n = 8)	TFV (n = 8)
	DRV/c Cohort 3 (N = 9)				
AUC_{tau} (h*ng/mL)	141,700	14,659	26,020	NA (AUC_{last}: 349)	1,159
C_{max} (ng/mL)	14,400	2,141	4,540	405	66
C_{tau} (ng/mL)	2,796	42	91	NA	37
	Adult DRV/COBI/F/TAF[5]				
AUC_{24h} (h*ng/mL)	87,909* 85,972†	8,745‡	11,918‡	132*	339‡
C_{max} (ng/mL)	8,826‡	1,129‡	2,056‡	163‡	19‡
C_{0h} (ng/mL)	1,899* 1,813†	31‡	93‡	NA	12‡

*From population PK analysis in Phase 3 study of DRV/COBI/F/TAF (TMC114FD2HTX3001) in ARV-naïve participants (N = 355); †From population PK analysis in Phase 3 study of DRV/COBI/F/TAF (TM114IFD3013) in ARV-experienced participants; ‡From Phase 2 PK substudy (N = 21) GS-US-299-0102

- Preliminary analysis based on limited PK data
- Limitation: Comparison between exposures from noncompartmental analyses (pediatric) and population PK analysis (adult)

Overall Safety

Table 3. Adverse Events

Adverse Events, n (%)	Cohort 3: F/TAF + DRV/c (N = 9)
Any AE	9 (100)
AE occurring in > 1 participant	
Iron-deficiency anemia	2 (22)
Vomiting	3 (33)
Drug-related AEs	
Tinea capitis	1 (11)*
Vomiting	1 (11)*
Serious AE	0
Drug-related serious AE	0
AE leading to premature discontinuation	0
Death	0

*Considered by the investigator to be related to the study drugs

- All AEs were mild or moderate in severity

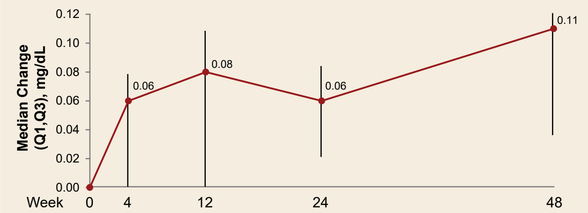
Laboratory Abnormalities

- Most treatment-emergent laboratory abnormalities were Grade 1 (2 [22%]) or 2 (6 [67%])
- One participant had two Grade 3 laboratory abnormalities at Week 4 of hypomagnesemia (0.83 mg/dL) and hyperkalemia (6.6 mEq/L); both were transient and resolved by Week 8

Abbreviations: ARV, antiretroviral; AE, adverse event; ATV, atazanavir; AUC_{24h}, area under the curve up to 24 hours; AUC_{last}, area under the curve up to the last measurable concentration; AUC_{tau}, area under concentration vs. time curve over dosing interval; c or COBI, cobicistat; C_{0h}, initial concentration; C_{max}, maximum observed plasma drug concentration; C_{tau}, observed drug concentration at end of dosing interval; DRV, darunavir; EFV, efavirenz; $eGFR_{Schwartz}$, estimated glomerular filtration rate by Schwartz equation; F or FTC, emtricitabine; GLSM, geometric least squares mean; IDMC, independent data monitoring committee; INSTI, integrase strand transfer inhibitor; iPK, intensive pharmacokinetic; LPV, lopinavir; mEq, milliequivalent; NA, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetic; Q, quartile; r, ritonavir; TAF, tenofovir alafenamide; TFV, tenofovir

Figure 5. Change From Baseline in $eGFR_{Schwartz}$

Figure 6. Change From Baseline in Serum Creatinine



Conclusions

- Interim data in virologically suppressed children aged ≥ 3 years and weighing between 14 and < 25 kg:
  - DRV, COBI, FTC, TAF and TFV exposures were within the range of exposures observed in adult studies
  - F/TAF plus DRV/c maintained viral suppression through 48 weeks of treatment
  - F/TAF plus DRV/c was well tolerated with no serious AEs or AEs that led to discontinuation or death
- To date, findings support the continuing evaluation of F/TAF as the NRTI backbone in combination with DRV/c in children with HIV

Next Steps

- Enrollment is ongoing in Cohorts 2 (≥ 6 to < 12 years; ≥ 25 to < 35 kg) and 3 (≥ 3 years; 14 to < 25 kg) to complete evaluation of F/TAF plus ATV or DRV boosted with COBI
- Population PK models will be developed once cohorts are fully enrolled to facilitate more appropriate comparisons
- Tablet-for-oral-suspension formulations of F/TAF and COBI have been developed; this formulation, with or without PI, is being evaluated for efficacy and safety in children aged ≥ 4 weeks and weighing ≥ 3 kg

References: **1.** Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf (accessed Jan 2023); **2.** Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach. Geneva: World Health Organization; 2021; **3.** Zhao AV, et al. Retrovirology 2022;19:22; **4.** Clinicalinfo.HIV.gov. Drug database: Cobicistat. June 2022. Available at: https://clinicalinfo.hiv.gov/en/drugs/cobicistat/patient (accessed Jan 2023); **5**. F/TAF + DRV/c USPI 2018. Available at: https://www.accessdata.fda.gov (accessed Jan 2023)

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