SAFETY AND PK OF LONG-ACTING CABOTEGRAVIR AND RILPIVIRINE IN ADOLESCENTS

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Carolyn Bolton Moore[1], Edmund Capparelli[2], Katherine Calabrese[3], Brookie M. Best[2], Shawn Ward[4], Cindy McCoig[5], Herta Crauwels[6], Allison Agwu[7], Pearl Samson[4], Barbara Heckman[4], Susan L. Ford[8], Adeola Adeyeye[9], Andres Camacho-Gonzalez[10], Jack Moye[11], Aditya H. Gaur[12]

[1]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [2]University of California San Diego, La Jolla, CA, United States, [3]FHI 360, Durham, NC, United States, [4]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, United States, [5]ViiV Healthcare, Collegeville, PA, United States, [6]Janssen Research & Development, Beerse, Belgium, [7]The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [8]GlaxoSmithKline, Research Triangle Park, NC, United States, [9]National Institute of Allergy and Infectious Diseases, Baltimore, MD, United States, [10]Emory University, Atlanta, GA, United States, [11]National Institute of Child Health and Human Development, Bethesda, MD, United States, [12]St Jude Children's Research Hospital, Memphis, TN, United States

BACKGROUND

- Long-acting cabotegravir (CAB-LA) plus long-acting rilpivirine (RPV-LA) are approved for maintenance of viral suppression in adults with HIV-1 infection
- IMPAACT 2017 (MOCHA) is a phase I/II non-comparative, open-label study to confirm the dose and evaluate safety, tolerability, acceptability, and pharmacokinetics (PK) of oral (PO) CAB, CAB-LA, and RPV-LA in adolescents, ≥12 to <18 years, living with HIV-1

METHODS

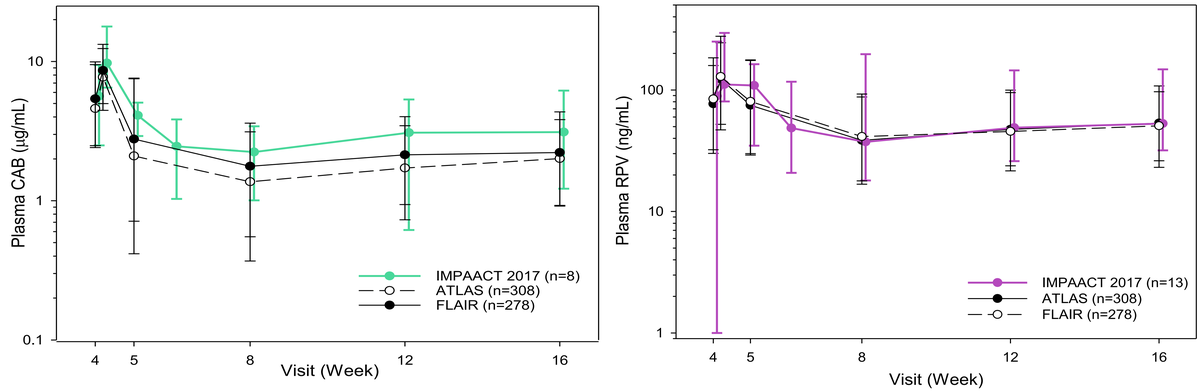
- Virologically suppressed (<50 copies/mL) adolescents with HIV-1 on stable combination antiretroviral therapy (ART) were enrolled into Cohort 1C (CAB) or Cohort 1R (RPV) based on background ART (background ART was continued throughout Cohort 1)
- Doses: 4 weeks of oral lead-in with CAB (30mg once daily) or RPV (25mg once daily), then CAB-LA (600mg/3mL at Week 4 and 400mg/2mL at Weeks 8 and 12) or RPV-LA (900mg/3mL at Week 4 and 600mg/2mL at Weeks 8 and 12) by gluteal intramuscular (IM) injection
- PK samples drawn at: Week 2 (oral dosing) and Weeks 4, 5, 6, 8, 12, 13, 14 and 16 (LA dosing)

TABLE 1. Baseline Characteristics (All-Treated Population)

	Cohort 1C (N=8)	Cohort 1R	Total (N=23)
Age in Years; Median (Q1,Q3)	14.5 (13.5, 17.0)	17.0 (15.0, 17.0)	16.0 (14.0,17.0)
Age; n (%)			
12 years	1 (12.5%)	1 (6.7%)	2 (8.7%)
13 years	1 (12.5%)	0	1 (4.3%)
14 years	2 (25.0%)	2 (13.3%)	4 (17.4%)
15 years	1 (12.5%)	1 (6.7%)	2 (8.7%)
16 years	0	3 (20.0%)	3 (13.0%)
17 years	3 (37.5%)	8 (53.3%)	11 (47.8%)
Sex at Birth; F/M, n (%)	2 (25.0%) / 6 (75.0%)	8 (53.3%) / 7 (46.7%)	10 (43.5%) / 13 (56.5%)
Race; n (%)			
Asian	1 (12.5%)	0	1 (4.3%)
Black/ African American	7 (87.5%)	11 (73.3%)	18 (78.3%)
White	0	4 (26.7%)	4 (17.4%)
Ethnicity; n (%)			
Hispanic or Latino	0	3 (20.0%)	3 (13.0%)
Weight in kg Median (Q1, Q3)	57.2 (44.2, 71.7)	63.0 (54.0, 75.0)	63 (47.7, 72.4)

Long-acting cabotegravir and rilpivirine, when given individually, in conjunction with background ART, were well tolerated in adolescents and achieved drug concentrations similar to those seen in adults.

Figure 1: Observed preliminary median (5th, 95th percentile) concentration-time data in adolescents (MOCHA) compared to pivotal Phase 3 Studies ATLAS and FLAIR in adults following oral lead in and 3 x monthly injections (CAB left panel, RPV right panel)



RESULTS

- Data per freeze date (10 Sept 2021): 23 participants enrolled (Table 1)
  - Cohort 1R: two premature treatment discontinuations; one due to hypersensitivity (after 1st oral dose, no systemic symptoms) and one due to pain with needle insertion prior to receiving first IM injection
- All participants to date were virally suppressed at Week 16 (Table 2)
- Injection site reactions were grade 1 or 2; none led to treatment discontinuation. One Grade 3 drug-related AE per cohort (Table 3- 1C: insomnia (day 41), 1R: hypersensitivity (day 1) leading to study withdrawal)
- Median (range) PK parameters met study targets with Q4 dosing (Figures 1 and 2)
  - Cohort 1C Week 2 Oral CAB $AUC_{0\text{-}T}$: 160 (94.3-325) mcg*h/mL (target median 46-277)
  - Week 16 IM CAB trough: 3.11 (range 1.22-6.19) mcg/mL (target median 0.71-6.7)
  - Cohort 1R Week 16 IM RPV trough: 52.9 (range 31.9-148) ng/mL (target median 25-100)

Table 2: Viral Suppression through Week 16 (All-Treated Population)

Analysis Visit	HIV-1 RNA <50 copies/mL; n (%)	HIV-1 RNA ≥50 copies/mL; n (%)	Total; n (%)
Cohort 1C (N=8)			
Baseline	8 (100.0)	0	8 (100.0)
Week 2	8 (100.0)	0	8 (100.0)
Week 4b	8 (100.0)	0	8 (100.0)
Week 8	7 (87.5)	1 (12.5)	8 (100.0)
Week 12	8 (100.0)	0	8 (100.0)
Week 16	7 (100.0)	0	7 (100.0)
Cohort 1R (N=15)			
Baseline	14 (93.3)	1 (6.7)	15 (100.0)
Week 2	14 (100.0)	0	14 (100.0)
Week 4b	13 (92.9)	1 (7.1)	14 (100.0)
Week 8	13 (100.0)	0	13 (100.0)
Week 12	13 (100.0)	0	13 (100.0)
Week 16	13 (100.0)	0	13 (100.0)

Table 3: Drug-related Adverse Events through Week 16 (Evaluable Population)

System Organ Class	Cohort 1C (N=8)			Cohort 1R (N=13)		
Grade*; n (%)	1	2	3	1	2	3
Number of participants with ≥ one adverse events	1 (12.5)	3 (37.5)	1 (12.5)	5 (38.5)	3 (23.1)	1 (7.7)
Diarrhoea	1 (12.5)	0	0	0	0	0
Nausea	0	0	0	1 (7.7)	0	0
General disorders	2 (25.0)	3 (37.5)	0	5 (38.5)	3 (23.1)	0
Injection site hypoaesthesia	0	0	0	1 (7.7)	0	0
Injection site nodule	0	0	0	1 (7.7)	0	0
Injection site pain	2 (25.0)	3 (37.5)	0	5 (38.5)	3 (23.1)	0
Injection site swelling	0	0	0	1 (7.7)	0	0
Immune system disorders	0	0	0	0	0	1 (7.7)
Drug hypersensitivity	0	0	0	0	0	1 (7.7)
Decreased appetite	1 (12.5)	0	0	0	0	0
Dizziness	0	0	0	1 (7.7)	0	0
Headache	1 (12.5)	0	0	0	0	0
Insomnia	0	0	1 (12.5)	1 (7.7)	0	0
Papular rash	0	0	0	1 (7.7)	0	0

*Grade 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Potentially Life-Threatening, 5 = Death; No Grade 4 or 5 AEs were reported in either Cohort.

CONCLUSIONS

- IM administration of CAB-LA or RPV-LA in adolescents achieved target exposure concentrations consistent with predictions and comparable to those observed in adults receiving monthly intra-muscular dose regimens.
- No new or unanticipated safety concerns were identified.

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