CABOTEGRAVIR AND RILPIVIRINE PK FOLLOWING LONG-ACTING HIV TREATMENT DISCONTINUATION

Susan L. Ford,[1] Herta Crauwels,[2] Kelong Han,[3] Stefaan Rossenu,[2] Feifan Zhang,[3] Jenny Huang,[4] David Margolis,[5] Kenneth Sutton,[5] Krischan Hudson,[5] Peter Williams,[2] William Spreen,[5] Parul Patel[5]

[1]GlaxoSmithKline, Research Triangle Park, NC, USA; [2]Janssen Research and Development, Beerse, Belgium; [3]GlaxoSmithKline, Upper Providence, PA, USA; [4]GlaxoSmithKline, Mississauga, ON, Canada; [5]ViiV Healthcare, Research Triangle Park, NC, USA

Introduction

- Long-acting (LA) regimens of the integrase inhibitor cabotegravir (CAB) + the non-nucleoside RT inhibitor rilpivirine (RPV) given monthly or every 2 months are in development for maintenance of HIV suppression.
- Both products exhibit absorption-rate limited pharmacokinetics (PK) following intramuscular (IM) administration, with mean apparent half-life (t1/2) estimates of 5.6-11.5 weeks (CAB) and 28 weeks (RPV).
- Following LA treatment discontinuation, CAB and RPV may remain measurable in plasma for a year or longer.
- PK data from HIV-infected subjects in the long-term follow-up (LTFU) of Phase 2b/3 studies (LATTE-2/ATLAS) are presented.

Methods

- Subjects who received CAB LA + RPV LA every 4 (Q4W, n=33) or every 8 (Q8W, n=5) weeks and withdrew for any reason were switched to alternative antiretroviral therapy (ART) and entered LTFU (1 year).[1,2]
- PK sampling occurred at 1, 3, 6, 9 and 12 months after final CAB LA + RPV LA IM injections.
- Plasma CAB and RPV concentrations were determined by validated LC-MS/MS assays (LLOQ 0.025 µg/mL and 1 ng/mL, respectively).
- RPV concentrations in subjects receiving oral RPV as part of their alternative regimen in LTFU were excluded from the results.
- Individual CAB and RPV LTFU concentrations are shown in comparison to respective LLOQ and in vitro protein adjusted IC90 (PA-IC90) values.
- Where possible, terminal slopes during LTFU were determined to approximate absorption rate constants and estimate associated half-lives.

Results

Figure 1. Number of Injection Visits Before Subjects Entered LTFU

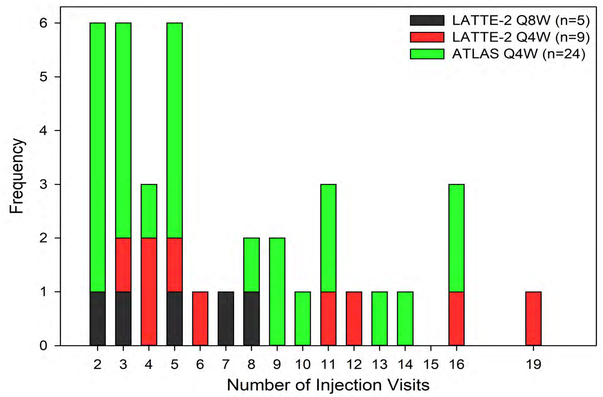


Table 1. Subject Demography and LTFU Alternative ART

Parameter		LATTE-2 (P2b) (n=14)	ATLAS (P3) (n=24)	Overall (n=38)
Study Regimen	Q4W	9	24	33
	Q8W	5	NA	5
Sex	Female	1	8	9
	Male	13	16	29
Age (years) (median, range)		34.5 (21 - 48)	38 (21 - 51)	37.5 (21 - 51)
Baseline Weight (kg) (median, range)		72.3 (52.7 - 95.0)	71.6 (41.2 - 120)	72.3 (41.2 - 120)
Baseline BMI (kg/m^2) (median, range)		24.2 (19.4 - 29.3)	23.3 (15.3 - 37.9)	23.7 (15.3 - 37.9)
LTFU ART[a]	Rilpivirine (oral)	1	6	7
	Dolutegravir	7	5	12
	Elvitegravir[b]	2	3	5
	Raltegravir	0	3	3
	Efavirenz	0	4	4
	Darunavir[b]	4	1	5
	Lopinavir[b]	0	3	3
	Atazanavir[b]	0	2	2
	Unspecified	2	0	2

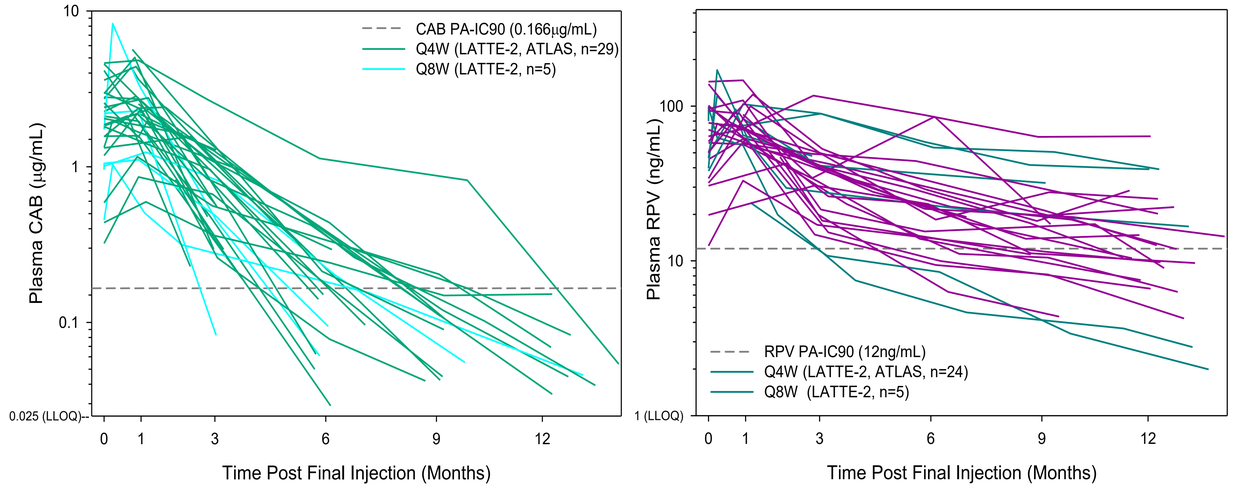
[a]Some individuals used multiple different ART regimens throughout the LTFU.
[b]Co-administered with boosting agents ritonavir or cobicistat except for 1 on atazanavir.

Table 2. Median (5th, 95th Percentile) Parameter Estimates of Individual LTFU Concentration-Time Data (Figure 2)

Parameter	CAB (n=34)	RPV (n=27)
Slope (hr^{-1})	0.00064 (0.00028, 0.00183)	0.00014 (0.00008, 0.0003)
Half-life (weeks)[a]	6.4 (2.3, 14.7)[a]	29.6 (15.2, 56.7)[a]

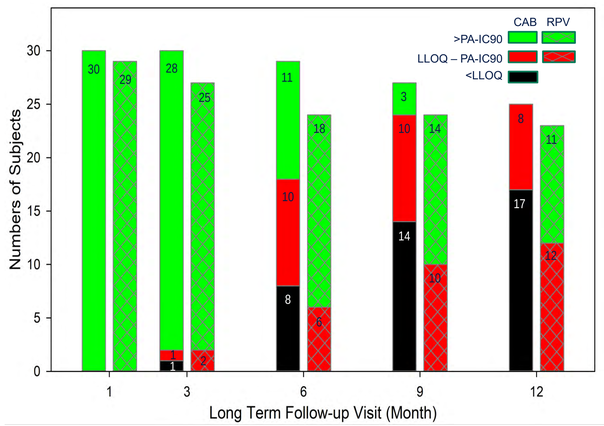
[a]Apparent terminal phase half-life should be interpreted with caution as data were insufficient (<2 half-life lengths) for accurate estimation in some profiles.

F



LLOQ, lower limit of quantification; PA-IC90, protein adjusted IC90.

Figure 3. Range of CAB (left) and RPV (right) Concentrations by LTFU Visit Following Discontinuation of Q4W and Q8W Regimens



Discussion

- CAB and RPV PK observed during the one-year LTFU phase of P2b/3 studies is consistent with the respective absorption-rate limited half-life of each product.
- CAB and RPV have low drug interaction potential as perpetrators and pose no PK-related limitations to alternative ART selection after discontinuation of injections.
- Use of UGT1A1 and/or CYP3A enzyme inhibitors or inducers could, respectively, decrease or increase the CAB and/or RPV systemic clearance, while ongoing absorption of residual drug from the injection sites remains unaffected.
- Adverse events were uncommonly reported, and no patients met CVF criteria during LTFU on alternative ART, which included integrase inhibitor–, NNRTI-, and protease inhibitor–based regimens.

Conclusions

Alternative ART selection after discontinuing CAB LA + RPV LA is unrestricted with respect to drug interactions and may include CYP3A and/or UGT1A1 inducers or inhibitors without efficacy or safety concerns.

Acknowledgments: This study was funded by ViiV Healthcare. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

References: 1. Margolis D, et al. *Lancet.* 2017;390:1499-1510. **2.** Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475.