COMPARABILITY OF 48-WEEK EFFICACY AND SAFETY OF CABOTEGRAVIR AND RILPIVIRINE LONG-ACTING EVERY 8 WEEKS TO STANDARD OF CARE IN SUPPRESSED PEOPLE LIVING WITH HIV-1

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Introduction

- Despite the success of daily oral antiretroviral therapy (ART), challenges still exist in some people living with HIV around stigma, pill burden, drug/food interactions and adherence. Therefore, there is considerable interest in developing long-acting (LA) therapeutics for HIV-1 infection.
- Cabotegravir (CAB), an integrase strand transfer inhibitor (INSTI), and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), are currently under development as an LA, injectable, two-drug regimen (CAB + RPV LA) for the maintenance of virologic suppression in people living with HIV-1.
- Noninferiority of CAB + RPV LA administered every 4 weeks (Q4W) in maintaining virologic suppression compared with daily oral standard of care (SoC) has been demonstrated in two pivotal Phase 3 studies[1,2] (ATLAS [NCT02951052] and FLAIR [NCT02938520]).
- Additionally, the ATLAS-2M (NCT03299049) Phase 3b study demonstrated the noninferiority of CAB + RPV LA administered every 8 weeks (Q8W) versus Q4W, with participants preferring the Q8W dosing over daily oral SoC and the Q4W regimen.[3,4]
- To date, no randomised Phase 3 clinical trial has directly compared CAB + RPV LA Q8W to daily oral SoC regimens. This indirect comparison of the ATLAS, FLAIR and ATLAS-2M trials assessed comparability of CAB + RPV LA Q8W with SoC.

Objective and Endpoints

Objective

- To compare the efficacy and safety of CAB + RPV LA Q8W versus once-daily oral SoC ART regimens for the maintenance of virologic suppression by an indirect comparison using data from the ATLAS, FLAIR and ATLAS-2M trials.

Endpoints

- Quantitative comparison of the following outcomes at Week 48:
  - Snapshot virologic suppression (<50 copies/mL) (Food and Drug Administration [FDA] Snapshot algorithm)
  - Snapshot virologic nonresponse (≥50 copies/mL) (FDA Snapshot algorithm)
  - Participants with no virologic data (FDA Snapshot algorithm)
  - Discontinuations due to adverse events (and no virologic data)
  - Mean CD4+ cell count change from baseline
  - Incidence of Grade 3 and Grade 4 non–injection site reaction (ISR) AEs.

Methods

Study Design

- An anchored indirect treatment comparison of CAB + RPV LA Q8W with daily oral SoC was conducted using Bucher's methodology according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines,[5] with CAB + RPV LA Q4W as the common comparator (**Figure 1**).
- To satisfy the similarity assumption as per ISPOR guidelines,[5] pooled data from ATLAS and FLAIR and the ATLAS-2M subgroup with no prior CAB + RPV LA exposure were used to inform the analysis, given the similarity in baseline participant characteristics.

Figure 1. Diagram of Studies Included in the Indirect Comparison

CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks, Q8W, every 8 weeks; RPV, rilpivirine; SoC, standard of care.

- The study characteristics of ATLAS, FLAIR and ATLAS-2M are shown in **Table 1**.

Table 1. Study Characteristics of the Phase 3, Multicentre, Open-Label ATLAS, FLAIR and ATLAS-2M Trials

Author, Year	Trial Acronym	Dosing Regimen and n	Population	Primary Outcome
Swindells, 2020[1]	ATLAS	CAB + RPV LA Q4W (n=308) SoC (any cART*) (n=308)	• ART experienced; suppressed prior to randomisation	• Switching to CAB + RPV LA Q4W was noninferior to continuing cART* over 48 weeks
Orkin, 2020[2]	FLAIR	CAB + RPV LA Q4W (n=283) SoC (DTG/ABC/3TC†) (n=283)	• ART naive; suppressed prior to randomisation	• Switching to CAB + RPV LA Q4W was noninferior to continuing DTG/ABC/3TC† over 48 weeks
Overton, 2020[3,4]	ATLAS-2M	CAB + RPV LA Q4W (n=523) CAB + RPV LA Q8W (n=522)	• ART experienced; suppressed prior to randomisation	• CAB + RPV LA Q8W was noninferior to CAB + RPV LA Q4W over 48 weeks

*Acceptable current antiretroviral regimens included two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) plus one of the following drugs: an INSTI, an NNRTI, a boosted protease inhibitor (PI), or unboosted atazanavir.
†If any participant had toxicity or intolerability in association with DTG/ABC/3TC, one switch to an approved alternative background NRTI was permitted. Participants who were positive for HLA-B*5701 received DTG plus two alternative non-ABC NRTIs instead of DTG/ABC/3TC.
3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; cART, combination antiretroviral therapy; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SoC, standard of care.

Statistical Analyses

- CAB + RPV LA Q8W and SoC were compared through a generalisation of Bucher's methodology to calculate relative risk (RR), odds ratio (OR) and risk difference (RD) values using CAB + RPV LA Q4W as the common comparator.

The indirect treatment effect estimates in terms of ln(RR), ln(OR) and RD are constructed from the corresponding direct randomised treatment effects:

Indirect treatment effect (Q8W vs. SOC) = Treatment effect (Q8W vs. Q4W) – Treatment effect (Q4W vs. SoC)

The associated standard error (SE) is calculated from the SE in each direct randomised estimate:

SE (Indirect treatment effect) = $(SE\text{ (Treatment effect [Q4W vs. SoC])}^2 + SE\text{ (Treatment effect [Q8W vs. Q4W])}^2)^{0.5}$

- Comparison statistics are shown in **Table 2**.

Table 2. Statistics for Treatment Effect (Treatment 1 vs. Treatment 2)

Binary Outcomes	Mean Statistic	Standard Error
Odds ratio (OR)	$\frac{r_2/(n_2-r_2)}{r_1/(n_1-r_1)}$	$\sqrt{\frac{1}{r_1}+\frac{1}{(n_1-r_1)}+\frac{1}{r_2}+\frac{1}{(n_2-r_2)}}$
Relative risk (RR)	$\frac{r_2/n_2}{r_1/n_1}$	$\sqrt{\frac{1}{r_1}-\frac{1}{n_1}+\frac{1}{r_2}-\frac{1}{n_2}}$
Risk difference (RD)	$\frac{r_2}{n_2}-\frac{r_1}{n_1}$	$\sqrt{\frac{\frac{r_1}{n_1}\left(1-\frac{r_1}{n_1}\right)}{n_1}+\frac{\frac{r_2}{n_2}\left(1-\frac{r_2}{n_2}\right)}{n_2}}$
Mean difference	$\mu_2-\mu_1$	$\sqrt{SE2^2+SE1^2}$

n, total number of people; r, number of people with event; SE, standard error; μ, mean.

Results

Table 3. Baseline Characteristics of ATLAS/FLAIR and ATLAS-2M Participants

	ATLAS/FLAIR		ATLAS-2M*	
Parameter	**SoC (n=591)**	**CAB + RPV LA Q4W (n=591)**	**CAB + RPV LA Q8W (n=327)**	**CAB + RPV LA Q4W (n=327)**
Age, median (range) years	38 (18–82)	38 (19–74)	41 (20–83)	42 (19–67)
Male (sex at birth), n (%)	423 (72)	429 (73)	254 (78)	252 (77)
Race, n (%)				
White	408 (69)	430 (73)	238 (73)	256 (78)
Black or African American	133 (23)	109 (18)	57 (17)	45 (14)
Asian	28 (5)	34 (6)	17 (5)	12 (4)
Other	20 (3)†	18 (3)	15 (5)	14 (4)
Ethnicity, n (%)				
Hispanic/Latino	74 (13)	63 (11)	54 (17)	42 (13)
Weight, mean (SD) kg	77.4 (17.0)	76.8 (15.3)	79.0 (15.9)	79.4 (17.3)
Body mass index, mean (SD) kg/m^2	25.9 (5.4)	25.7 (4.8)	26.2 (5.1)	26.2 (5.2)
CD4+ cell count, median (IQR) cells/μL	641 (480–821)	645 (487–824)	643 (496–849)	711 (535–886)
Baseline third active drug class, n (%)				
INSTI	382 (65)	385 (65)	136 (42)	141 (43)
NNRTI	155 (26)	155 (26)	151 (46)	156 (48)
PI	54 (9)	51 (9)	40 (12)	30 (9)

*Participants with prior CAB + RPV LA exposure in ATLAS-2M were excluded.
†In addition, two participants' data are missing.
CAB, cabotegravir; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SD, standard deviation; SoC, standard of care.

- Baseline characteristics were similar between ATLAS/FLAIR and ATLAS-2M (**Table 3**).
- An unmatched distribution of participants switching from INSTIs and NNRTIs to study treatment was observed between the pooled ATLAS/FLAIR and ATLAS-2M trials.
  - To mitigate any potential effects, a subgroup analysis of virologic suppression stratified by baseline third active drug class was planned to assess what impact the unmatched distribution had on the findings of the main analysis.

Table 4. Week 48 Efficacy and Safety Data From the Pooled ATLAS/FLAIR and ATLAS-2M Trials

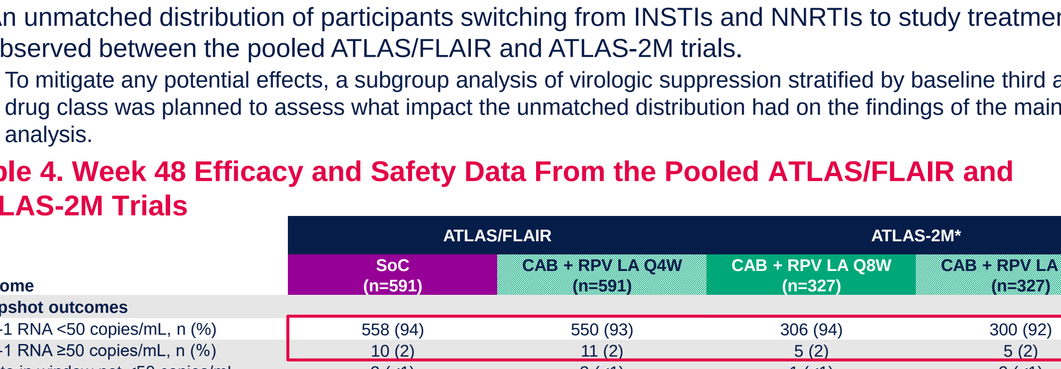
	ATLAS/FLAIR		ATLAS-2M*	
Outcome	**SoC (n=591)**	**CAB + RPV LA Q4W (n=591)**	**CAB + RPV LA Q8W (n=327)**	**CAB + RPV LA Q4W (n=327)**
Snapshot outcomes				
HIV-1 RNA <50 copies/mL, n (%)	558 (94)	550 (93)	306 (94)	300 (92)
HIV-1 RNA ≥50 copies/mL, n (%)	10 (2)	11 (2)	5 (2)	5 (2)
Data in window not <50 copies/mL	3 (<1)	3 (<1)	1 (<1)	2 (<1)
Discontinued for lack of efficacy	5 (<1)	7 (1)	4 (1)	2 (<1)
Discontinued for other reasons while not <50 copies/mL	2 (<1)	1 (<1)	0	1 (<1)
No virologic data, n (%)	23 (4)	30 (5)	16 (5)	22 (7)
Discontinued for AEs	6 (1)	19 (3)	6 (2)	11 (3)
Discontinued due to death	1 (<1)†	0	0	0
Discontinued for other reasons	16 (3)	11 (2)	10 (3)	11 (3)
Other efficacy outcomes				
Mean CD4+ cell count change from baseline (SD), cells/μL	48.2 (182.1)	24.5 (191.3)	–0.7 (150.6)	–19.2 (204.9)
Safety outcomes				
Discontinued for AEs, n (%)	7 (1)	19 (3)	6 (2)	11 (3)
Grade 3/4 non-ISR AEs, n (%)	35 (6)	47 (8)	16 (5)	20 (6)

*Participants with prior CAB + RPV LA exposure in ATLAS-2M were excluded.
†Death was due to a methamphetamine overdose and was considered not related to the study treatment.
AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SD, standard deviation; SoC, standard of care.

- A summary of the Week 48 efficacy and safety data used for the indirect treatment comparison is shown in **Table 4**.

CAB + RPV LA Q8W is Noninferior to Daily Oral SoC

Figure 2. Forest Plot of Risk Difference (95% CI) for CAB + RPV LA Q8W vs. SoC at Week 48

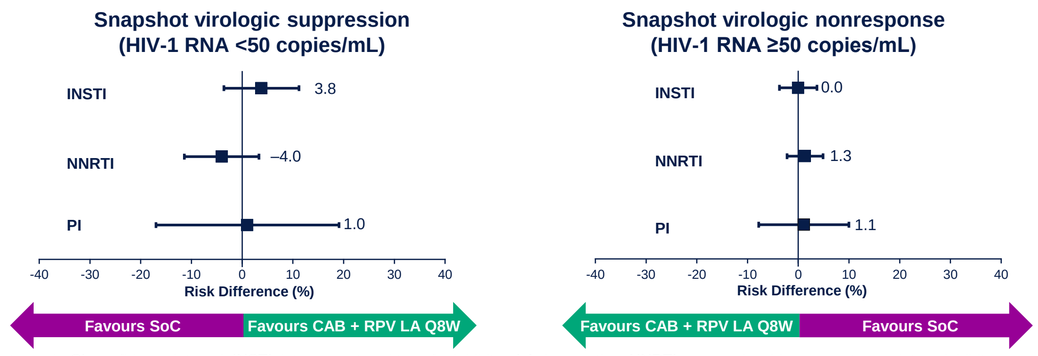


*Favours CAB + RPV LA Q8W.
†Mean difference.
‡Participants with no virologic data at Week 48 who discontinued due to AEs.
AE, adverse event; CAB, cabotegravir; CI, confidence interval; ISR, injection site reaction; LA, long-acting; Q8W, every 8 weeks; RPV, rilpivirine; SoC, standard of care.

- There were no significant differences in any of the key efficacy or safety outcomes analysed for CAB + RPV LA Q8W compared with daily oral SoC at Week 48 (**Figure 2**).
- This was consistent across all comparative effect measures assessed: relative risk, odds ratio and risk difference.

Baseline Third Active Drug Class had no Impact on the Main Analysis

Figure 3. Forest Plots of Risk Difference (95% CI) for CAB + RPV LA Q8W vs. SoC at Week 48 Stratified by Baseline Third Active Drug Class



CAB, cabotegravir; CI, confidence interval; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q8W, every 8 weeks; RPV, rilpivirine; SoC, standard of care.

- CAB + RPV LA Q8W versus daily oral SoC Snapshot virologic outcome comparisons were stratified by baseline third active drug class to assess the potential impact of the unmatched distribution of participants switching from INSTIs and NNRTIs to study treatment between the trials.
- Comparative effect measures consistently showed no significant differences in Snapshot virologic outcome for any of the baseline third active drug classes assessed, suggesting that the unbalanced distribution had no impact on the findings of the main analysis (**Figure 3**).

Conclusions

- These results support the therapeutic potential of CAB + RPV LA Q8W for virologically suppressed people living with HIV-1 who seek alternative options to daily oral combination ART.
- CAB + RPV LA Q8W demonstrated comparability in efficacy and safety with SoC consisting of guideline-recommended daily oral combination ART.

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References: 1. Swindells S, et al. *N Engl J Med.* 2020;382(12):1112–1123. **2.** Orkin C, et al. *N Engl J Med.* 2020;382(12):1124–1135. **3.** Overton ET, et al. CROI 2020; Virtual. Presentation 3334. **4.** Overton ET, et al. *Lancet*. Submitted 2020. **5.** Hoaglin DC, et al. *Value Health*. 2011;14(4):429–437.

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