THE LANCET
HIV

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Jaeger H, Overton ET, Richmond G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet HIV* 2021; published online Oct 11. http://dx.doi.org/10.1016/S2352-3018(21)00185-5.

Supplementary Material

Table S1. Baseline demographics and disease characteristics

	Q8W (n=522)	Q4W (n=523)
Age, median (IQR) years	42·0 (34–51)	42·0 (34–50)
Sex at birth		
Female	137 (26)	143 (27)
Male	385 (74)	380 (73)
Participant-reported gender		
Female	142 (27)	146 (28)
Male	380 (73)	377 (72)
Race		
White	371 (71)	393 (75)
Black/African American	100 (19)	90 (17)
Other	51 (10)	40 (8)
Hispanic/Latino ethnicity	70 (13)	65 (12)
Prior ART*		
NNRTI	368 (70)	382 (73)
INSTI	334 (64)	341 (65)
PI	116 (22)	111 (21)
Body mass index, median (IQR) kg/m^2	25·7 (23·0–29·1)	25·9 (23·1–28·9)
Weight, median (IQR) kg	77·5 (68·7–88·0)	78·0 (69·0–88·7)
Prior exposure to CAB+RPV LA[†]		
None	327 (63)	327 (63)
1–24 weeks	69 (13)	68 (13)
>24 weeks	126 (24)	128 (24)
CD4+ cell count, median (IQR) cells/mm^3	642 (499–827)	688 (523–878)
CD4+ cell category		
<350 cells/mm^3	35 (7)	27 (5)
350 to <500 cells/mm^3	96 (18)	89 (17)
≥500 cells/mm^3	391 (75)	407 (78)
Co-infection		
Hepatitis B virus[‡]	2 (<1)	1 (<1)
Hepatitis C virus	5 (<1)	6 (1)
Geographical distribution[§]		
Africa	40	42
Asia	87	78
Europe	190	175
North America	185	196
South America	12	17
Oceania	8	15
Comorbidities[¶]		
Hypertension	79 (15)	76 (15)
Hyperlipidemia	79 (15)	74 (14)
Insomnia	71 (14)	57 (11)
Concomitant non-ART medications[‖]		
Ibuprofen	185 (35)	194 (37)
Paracetamol	182 (35)	183 (35)
Influenza vaccine	104 (20)	129 (25)

Data are n (%) unless otherwise stated.

*Prior ART was recorded at screening and minor updates have been made since the Week 48 analysis.

[†]Overall exposure refers to oral CAB+RPV taken as oral lead-in or oral bridging, as well as previous CAB+RPV LA injections.

[‡]Participants classified as hepatitis B–positive could participate in the study based on clinical determination. These three participants were found to have hepatitis B DNA below the level of quantification but with HBV DNA reported as detected. All three had testing for HBV DNA taken at different timepoints at which it was no longer detected, and then were allowed to participate in the study.

[§]Africa included South Africa only (Q8W, n=40; Q4W, n=42). Asia included Republic of Korea (Q8W, n=18; Q4W, n=9) and Russian Federation (Q8W, n=69; Q4W, n=69). Europe included France (Q8W, n=26; Q4W, n=28), Germany (Q8W, n=48; Q4W, n=36), Italy (Q8W, n=26; Q4W, n=22), Spain (Q8W, n=77; Q4W, n=81), and Sweden (Q8W, n=13; Q4W, n=8). North America included Canada (Q8W, n=35; Q4W, n=41), Mexico (Q8W, n=10; Q4W, n=6), and the United States (Q8W, n=140; Q4W, n=149). South America included Argentina only (Q8W, n=12; Q4W, n=17). Oceania included Australia only (Q8W, n=8; Q4W, n=15).

[¶]The three most common comorbidities are presented.

[‖]The three most common concomitant non-ART medications are presented.

ART, antiretroviral therapy; CAB, cabotegravir; HBV, hepatitis B virus; 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.

Table S2. Summary of CAB and RPV plasma concentrations at SVF visit for participants with CVF

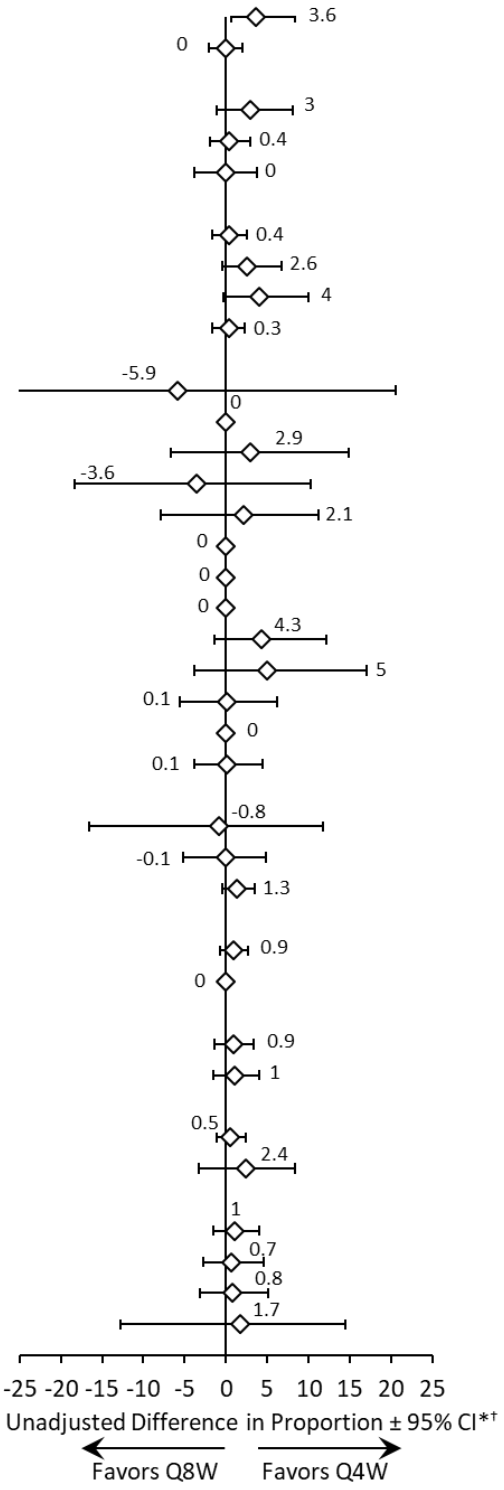
Regimen	CVF Participant number	SVF visit	Prior exposure to CAB + RPV (weeks)	CAB (µg/mL) at SVF visit	RPV (ng/mL) at SVF visit
Q8W	1*	8	1–24	1·1	74
	2[†]	16	0	0·65	14·2
	3*[‡]	16	0	1·35	34·8
	4	16	0	0.921	34·2
	5*	24	0	1·57	108
	6*	24	0	1·82	44.3
	7*	24	1–24	1·45	62·6
	8	48	1–24	1·44	78·5
	9	88	0	1·07	118
Q4W	10[§]	16	0	1·28	47·4
	11	32	0	1·99	52·9

*Major NNRTI RAMs at baseline. [†]CVF but not Snapshot failure, achieved <50 copies/mL at Week 20 visit. [‡]Major INSTI RAMs at baseline. [§]G190Q at baseline associated with a high level of resistance to RPV, not defined as RAM.

CAB, cabotegravir; CVF, confirmed virologic failure; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine; SVF, suspected virologic failure.

Figure S1. Summary of outcomes (plasma HIV-1 RNA ≥50 copies/mL at Week 96) by subgroup (maintenance phase), FDA Snapshot algorithm (ITT-E population)*,†

		Q8W, n/n (%)	Q4W, n/n (%)	
Sex at birth	Female	5/137 (4)	0/143 (0)	3.6
	Male	6/385 (2)	6/380 (2)	0
Age, years	<35	6/137 (4)	2/145 (1)	3
	35-49	3/242 (1)	2/239 (1)	0.4
	≥50	2/143 (1)	2/139 (1)	0
Race	White	7/371 (2)	6/393 (2)	0.4
	Non-white	4/151 (3)	0/130 (0)	2.6
	Black/Afr Amer	4/100 (4)	0/90 (0)	4
	Non-black/Afr Amer	7/422 (2)	6/433 (1)	0.3
Region	Argentina	0/12 (0)	1/17 (6)	-5.9
	Australia	0/8 (0)	0/15 (0)	0
	Canada	1/35 (3)	0/41 (0)	2.9
	France	0/26 (0)	1/28 (4)	-3.6
	Germany	1/48 (2)	0/36 (0)	2.1
	Italy	0/26 (0)	0/22 (0)	0
	Republic of Korea	0/18 (0)	0/9 (0)	0
	Mexico	0/10 (0)	0/6 (0)	0
	Russian Federation	3/69 (4)	0/69 (0)	4.3
	South Africa	2/40 (5)	0/42 (0)	5
	Spain	1/77 (1)	1/81 (1)	0.1
	Sweden	0/13 (0)	0/8 (0)	0
	United States	3/140 (2)	3/149 (2)	0.1
Baseline CD4+ cells/mm^3	<350	1/35 (3)	1/27 (4)	-0.8
	350 to <500	1/96 (1)	1/89 (1)	-0.1
	≥500	9/391 (2)	4/407 (1)	1.3
Baseline HIV-1 RNA, copies/mL	<50	11/519 (2)	6/513 (1)	0.9
	≥50	0/3 (0)	0/10 (0)	0
Prior exposure to CAB+RPV, weeks	0	8/327 (2)	5/327 (2)	0.9
	≥1	3/195 (2)	1/196 (1)	1
Baseline BMI, kg/m^2	<30	6/409 (2)	4/425 (1)	0.5
	≥30	5/113 (4)	2/98 (2)	2.4
Baseline 3rd agent class	CAB+RPV	3/195 (2)	1/196 (1)	1
	NNRTI	3/151 (2)	2/156 (1)	0.7
	INSTI	3/136 (2)	2/141 (1)	0.8
	PI	2/40 (5)	1/30 (3)	1.7

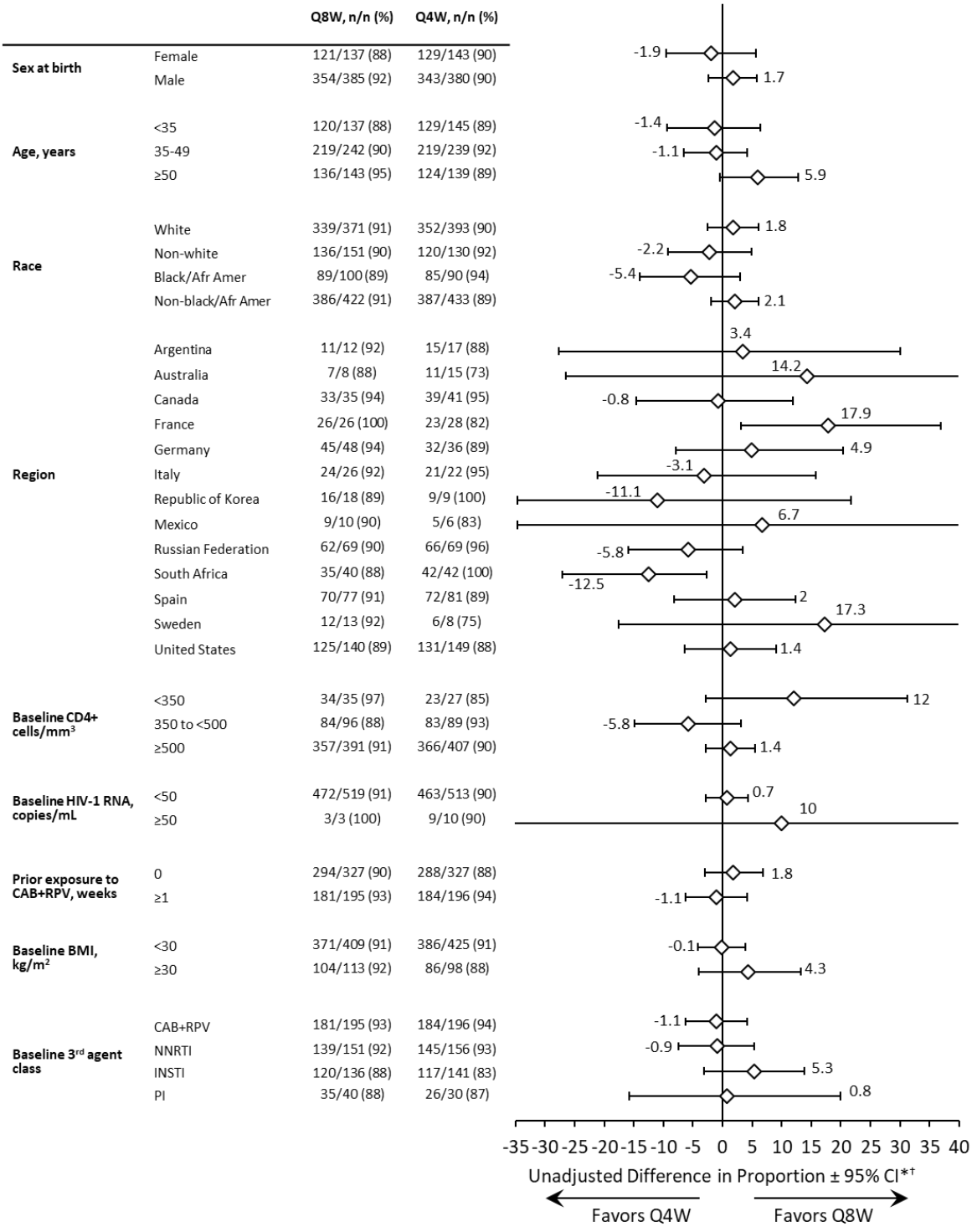


*Difference: proportion on Q8W – proportion on Q4W.

†95% CIs were calculated using an unconditional exact method with two inverted one-sided tests based on the score statistic.

BMI, body mass index; CAB, cabotegravir; CI, confidence interval; INSTI, integrase strand transfer inhibitor; ITT-E, intention-to-treat exposed; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Figure S2. Summary of outcomes (plasma HIV-1 RNA <50 copies/mL at Week 96) by subgroup (maintenance phase), FDA Snapshot algorithm (ITT-E population)*,†

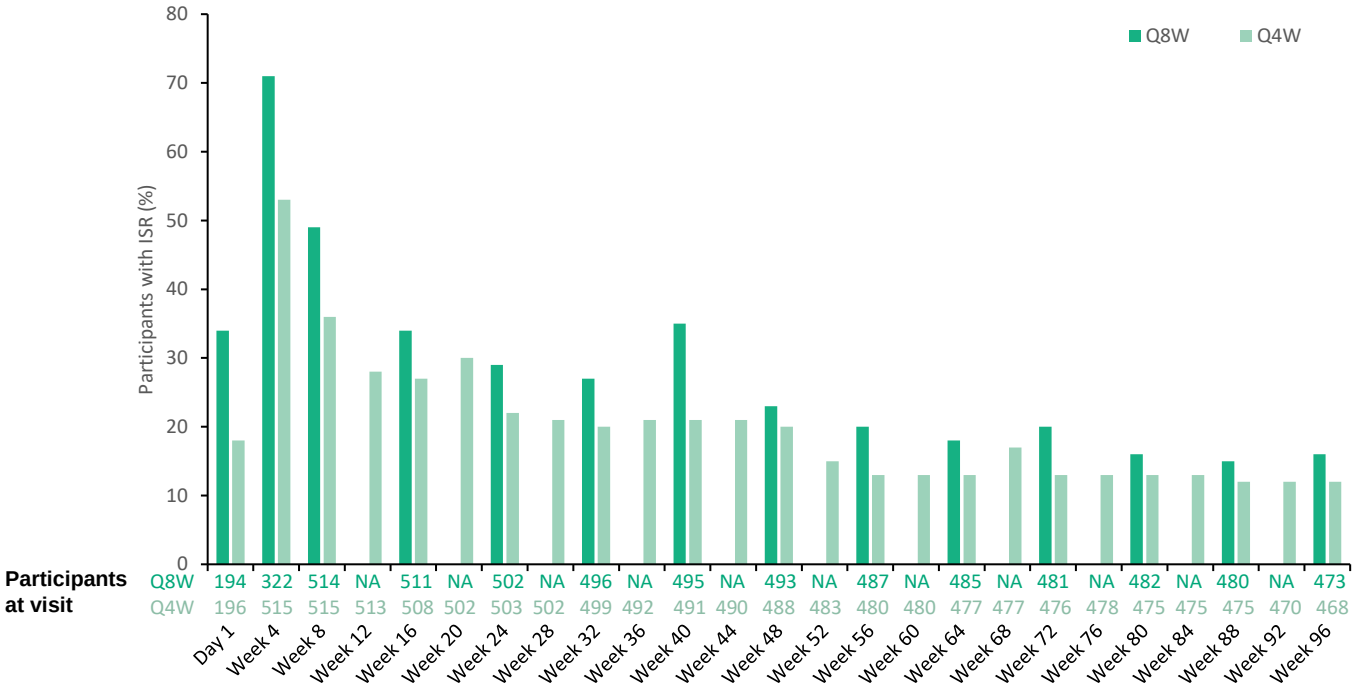


*Difference: proportion on Q8W – proportion on Q4W.

†95% CIs were calculated using an unconditional exact method with two inverted one-sided tests based on the score statistic.

BMI, body mass index; CAB, cabotegravir; CI, confidence interval; INSTI, integrase strand transfer inhibitor; ITT-E, intention-to-treat exposed; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

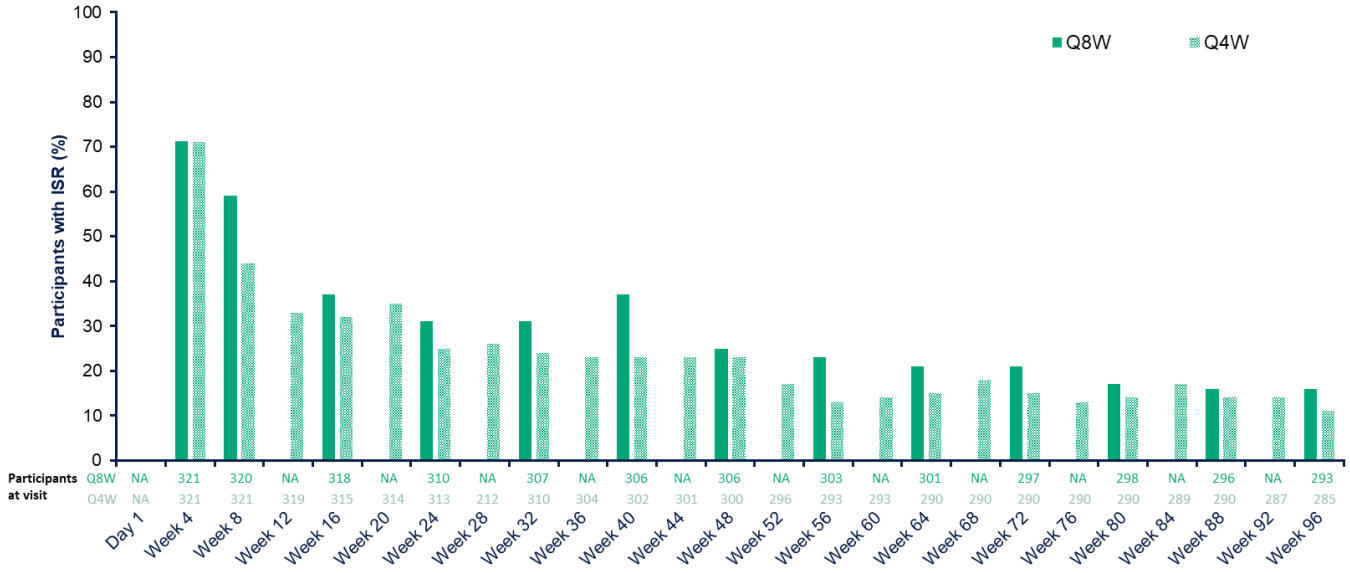
Figure S3. ISRs over time



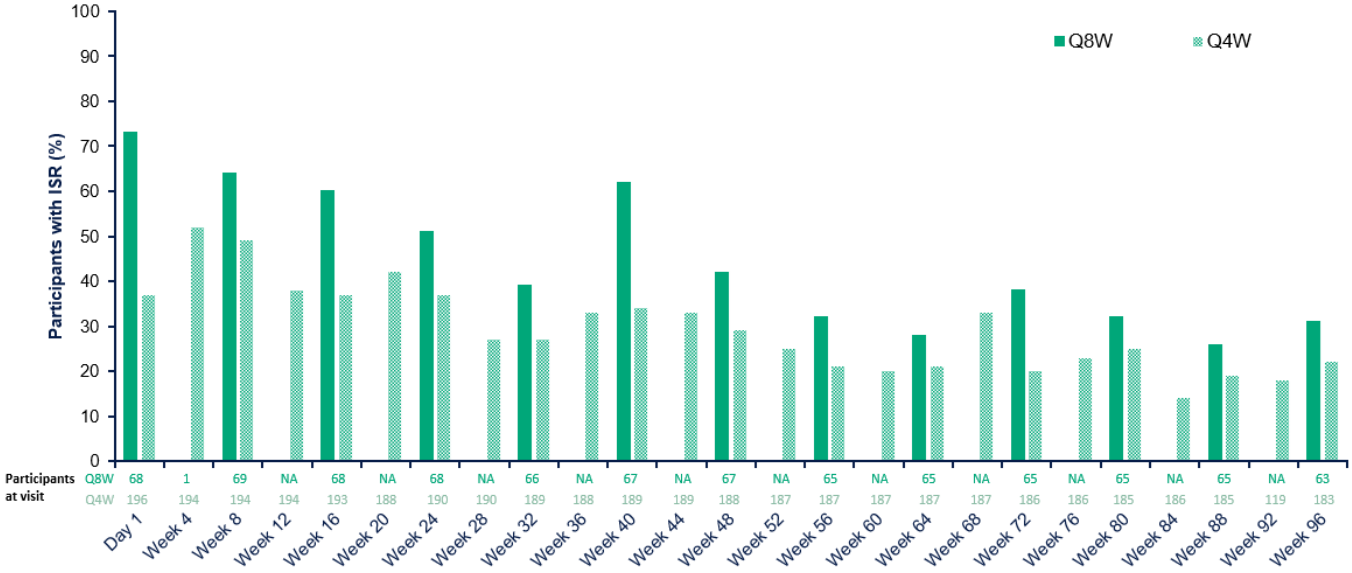
ISR, injection site reaction; NA, not applicable; Q4W, every 4 weeks; Q8W, every 8 weeks.

Figure S4. ISRs over time by prior exposure

a. ISRs over time in participants with no prior exposure to CAB+RPV



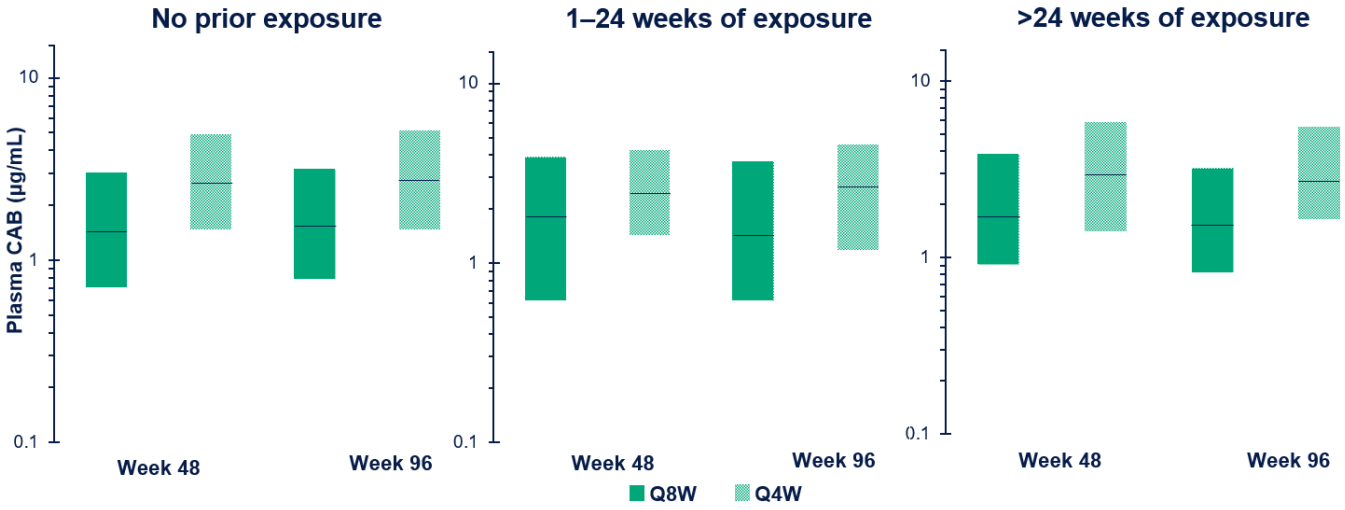
b. ISRs over time in participants with prior exposure to CAB+RPV



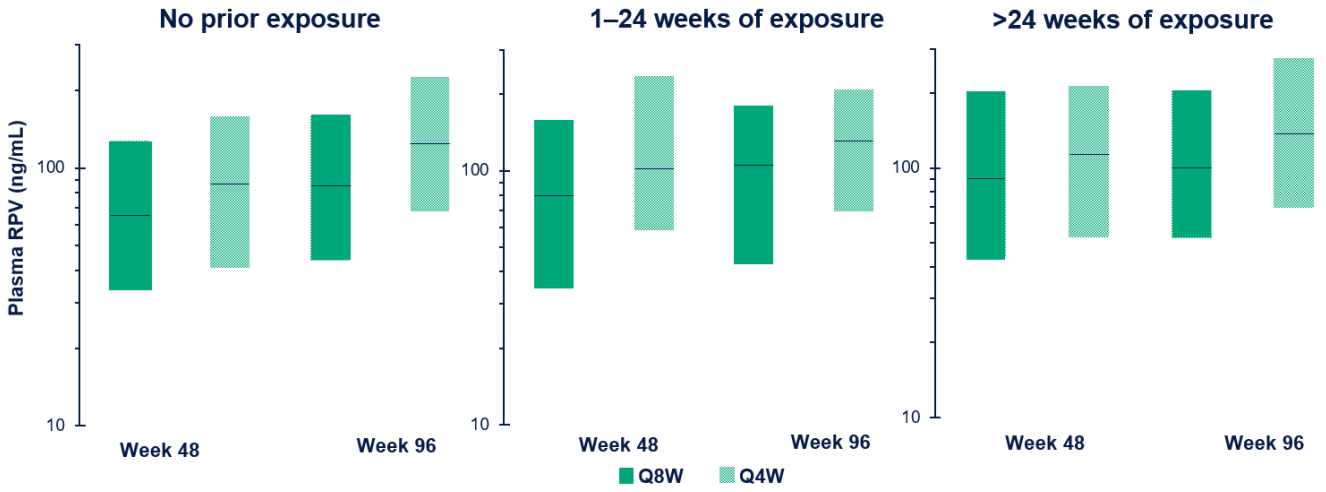
CAB, cabotegravir; ISR, injection site reaction; NA, not applicable; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Figure S5. CAB and RPV concentrations at Week 48 and Week 96 stratified by prior exposure

a. Plasma CAB concentrations at Week 48 and Week 96 stratified by prior exposure



b. Plasma RPV concentrations at Week 48 and Week 96 stratified by prior exposure



Bars represent the 5th and 95th percentiles; lines represent the medians.
CAB, cabotegravir; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.