Efficacy and Safety Outcomes by BMI Category Over 48 Weeks in Phase 3/3b Cabotegravir and Rilpivirine Long-Acting Trials

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Disclosure

- Emilie Elliot is an employee of ViiV Healthcare and stockholder of GlaxoSmithKline

Introduction

- Cabotegravir (CAB) + rilpivirine (RPV) is the first complete long-acting (LA) regimen recommended by the US DHHS and IAS–USA treatment guidelines for the maintenance of HIV-1 virologic suppression[1,2]
- CAB + RPV LA has demonstrated favorable efficacy and safety with a low 1% rate of confirmed virologic failure (CVF) when dosed monthly or every 2 months through 96 weeks across diverse subgroups[3–8]
- The global prevalence of overweight and obesity in people living with HIV has been rising and is associated with many comorbidities[9]
- Efficacy, safety, and pharmacokinetics (PK) of CAB + RPV LA are presented through Week 48 among Phase 3/3b trial participants, stratified by baseline body mass index (BMI) category

US DHHS, United States Department of Health and Human Services; IAS–USA, International Antiviral Society–United States of America.
1. US Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2021. Available from: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/15/virologic-failure. Accessed August 2021. 2. Saag MS, et al. *JAMA*. 2020;324(16):1651–1669. 3. Swindells S, et al. *N Engl J Med*. 2020;382(12):1112–1123. 4. Swindells S, et al. *AIDS*. Accepted 2021. 5. Orkin C, et al. *N Engl J Med*. 2020;382(12):1124–1135. 6. Orkin C, et al. *Lancet HIV*. 2021;8(4):e185–e196. 7. Overton ET, et al. *Lancet*. 2021;396(10267):1994–2005. 8. Jaeger H, et al. *Lancet HIV*. Accepted 2021. 9. Koethe JR, et al. *AIDS Res Hum Retroviruses.* 2016;32(1):50–58.

Methods

- Data were pooled for participants without prior exposure to CAB + RPV receiving CAB + RPV LA every 8 weeks (Q8W) or every 4 weeks (Q4W) in the ATLAS, FLAIR, and ATLAS-2M studies
- Participants were categorized by dosing regimen (Q8W vs. Q4W) and BMI category (lower, <30 kg/m^2; higher, ≥30 kg/m^2)

Endpoints Evaluated Through Week 48 by BMI Category

- The proportion of participants with plasma HIV-1 RNA ≥50 and <50 copies/mL
- The incidence of CVF (two consecutive HIV-1 RNA ≥200 copies/mL)
- Safety, including injection site reaction (ISR) adverse events (AEs)
- CAB and RPV plasma trough concentrations through Week 48

BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; LA, long-acting; RPV, rilpivirine.

Baseline Characteristics

ITT-E population	Pooled CAB + RPV LA participants across ATLAS, FLAIR, and ATLAS-2M			
	BMI <30 kg/m^2 (n=1032)		BMI ≥30 kg/m^2 (n=213)	
	Q8W (n=268)	Q4W (n=764)	Q8W (n=59)	Q4W (n=154)
Age, median (range) years	41 (20–83)	38 (19–68)	43 (32–71)	41 (23–74)
≥50 years, n (%)	73 (27)	148 (19)	16 (27)	37 (24)
Female (sex at birth), n (%)	48 (18)	172 (23)	25 (42)	65 (42)
Race, n (%)				
White	201 (75)	591 (77)	37 (63)	95 (62)
Black or African American	37 (14)	103 (13)	20 (34)	51 (33)
Asian	17 (6)	44 (6)	0	2 (1)
Other	13 (5)	26 (3)	2 (3)	6 (4)
Hispanic or Latinx ethnicity, n (%)	43 (16)	89 (12)	11 (19)	16 (10)
Weight, median (range) kg	74.0 (49.0–109.2)	73.2 (41.2–108.4)	98.0 (76.0–136.9)	99.9 (70.9–139.4)
BMI, median (range) kg/m^2	24.4 (17.8–30.0)	24.0 (15.3–29.9)	32.5 (30.1–46.0)	33.2 (30.0–54.0)
30–<40, n (%)	N/A	N/A	49 (83)	139 (90)
≥40, n (%)	N/A	N/A	10 (17)	15 (10)

- Among 1245 participants randomized to receive CAB + RPV LA, 213 (17%) had a BMI ≥30 kg/m^2 at baseline

BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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Viral Suppression Was High and Comparable Across BMI Categories

Parameter, n (%)	Pooled CAB + RPV LA participants across ATLAS, FLAIR, and ATLAS-2M			
	BMI <30 kg/m^2 (n=1032)		BMI ≥30 kg/m^2 (n=213)	
	Q8W (n=268)	Q4W (n=764)	Q8W (n=59)	Q4W (n=154)
HIV-1 RNA <50 copies/mL	252 (94)	708 (92.7)	54 (91.5)	142 (92.2)
HIV-1 RNA ≥50 copies/mL	1 (0.4)	9 (1.2)	4 (6.8)	7 (4.5)
Data in window not below threshold	1 (0.4)	1 (0.1)	0	4 (2.6)
Discontinued for lack of efficacy	0	6 (0.8)	4 (6.8)	3 (1.9)
Discontinued for other reason while not below threshold	0	2 (0.3)	0	0
No virologic data in Week 48 window	15 (5.6)	47 (6.2)	1 (1.7)	5 (3.2)
Discontinued due to AE or death	6 (2.2)	29 (3.8)	0	1 (0.6)
Discontinued for other reasons	9 (3.4)	18 (2.4)	1 (1.7)	4 (2.6)

- At Week 48, across both dosing regimens, 93–94% of participants in the lower BMI group had HIV-1 RNA <50 copies/mL vs. 92% in the higher BMI group
- Overall, 10 vs. 11 participants had HIV-1 RNA ≥50 copies/mL in the lower and higher BMI groups, respectively

AE, adverse event; BMI, body mass index; CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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No Participant With BMI ≥30 kg/m^2 As the Only Baseline Factor Met the CVF Criterion Through Week 48

	Pooled CAB + RPV LA participants across ATLAS, FLAIR, and ATLAS-2M	
	BMI <30 kg/m^2 (n=1032)	BMI ≥30 kg/m^2 (n=213)
CVF through Week 48, n	5*	8†
No other baseline factors, n	3	0‡
At least one other baseline factor, n	2	8
RPV resistance-associated mutations alone	0	3
HIV-1 subtype A6/A1 alone	1	4
Both	1	1

- Amongst 153§ participants with BMI ≥30 kg/m^2 as the only baseline factor, none met the CVF criterion
- CVF events were uncommon across all three Phase 3/3b studies through 48 weeks of CAB + RPV LA (n=13/1245, 1%)‖

*Q8W, n=1; Q4W, n=4. †Q8W, n=4; Q4W, n=4. ‡BMI ≥30 kg/m^2 was the only baseline risk factor. §Of the 213 participants with a BMI ≥30 kg/m^2, 185 had data available for HIV-1 subtype and RPV resistance-associated mutations; among the 28 participants who were missing data for one or both of the other baseline factors, none met the CVF criterion. ‖One participant had oral CAB + RPV dosing interrupted due to a false-positive pregnancy test and, upon reinitiation of oral therapy, had suspected virologic failure that was confirmed.
BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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Safety Summary (Excluding ISRs)

Parameter, n (%)	Pooled CAB + RPV LA participants across ATLAS, FLAIR, and ATLAS-2M			
	BMI <30 kg/m^2		BMI ≥30 kg/m^2	
	Q8W (n=268)	Q4W (n=764)	Q8W (n=59)	Q4W (n=154)
Any AE	211 (79)	656 (86)	41 (69)	127 (82)
Any Grade ≥3 AE	14 (5)	55 (7)	1 (2)	8 (5)
Any drug-related AE	66 (25)	218 (29)	8 (14)	43 (28)
Any Grade ≥3 drug-related AE	2 (<1)	12 (2)	0	0
AE leading to withdrawal	6 (2)	26 (3)	0	1 (<1)
Any serious AE*	13 (5)	30 (4)	2 (3)	5 (3)
Drug related	0	2 (<1)	0	0

- Drug-related Grade ≥3 AEs (excluding ISRs) were uncommon, occurring in <1% of participants across both BMI categories and dosing regimens

*None were fatal.
AE, adverse event; BMI, body mass index; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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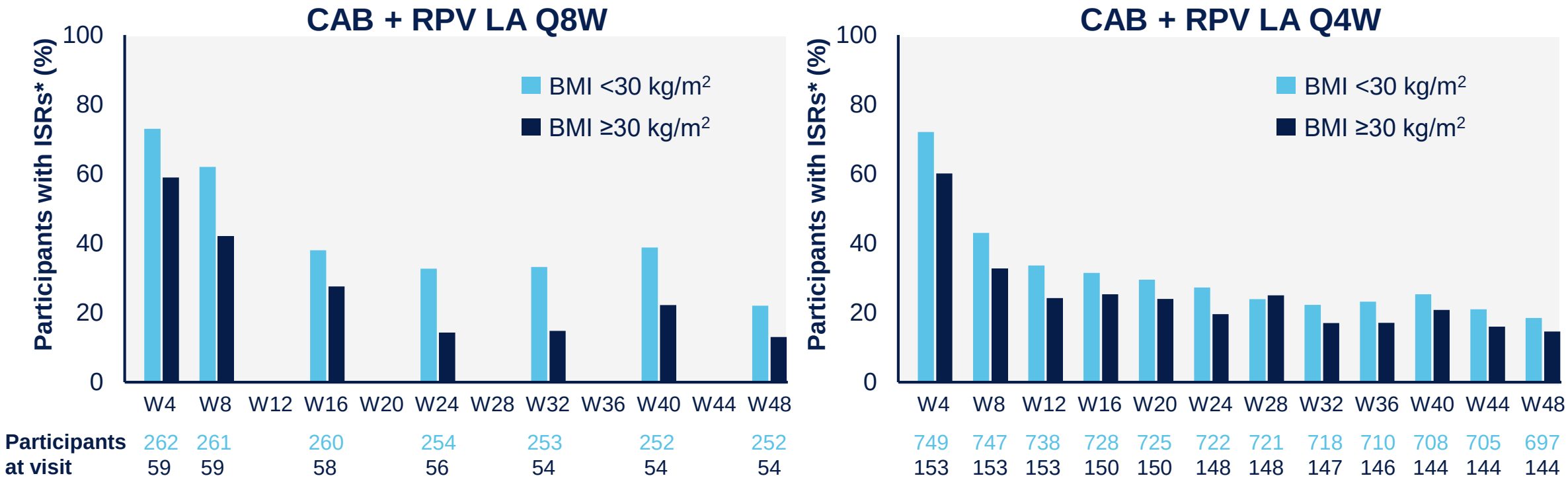
Most ISRs Were Mild or Moderate in Severity



- ISR incidence decreased over time regardless of BMI group or dosing regimen, with a numerical trend toward fewer ISRs in the higher BMI group
- The majority of ISRs were short-lived (median, 3 days), with injection site pain the most commonly reported (22% of all injections), regardless of BMI or dosing regimen

*AE grade is the maximum grade reported by the participant at each visit. Few ISRs were classified as Grade 3 (~1% of ISR events), consistent across both BMI categories and regimens. There were no Grade 4 or 5 ISR events.
AE, adverse event; BMI, body mass index; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; W, week.

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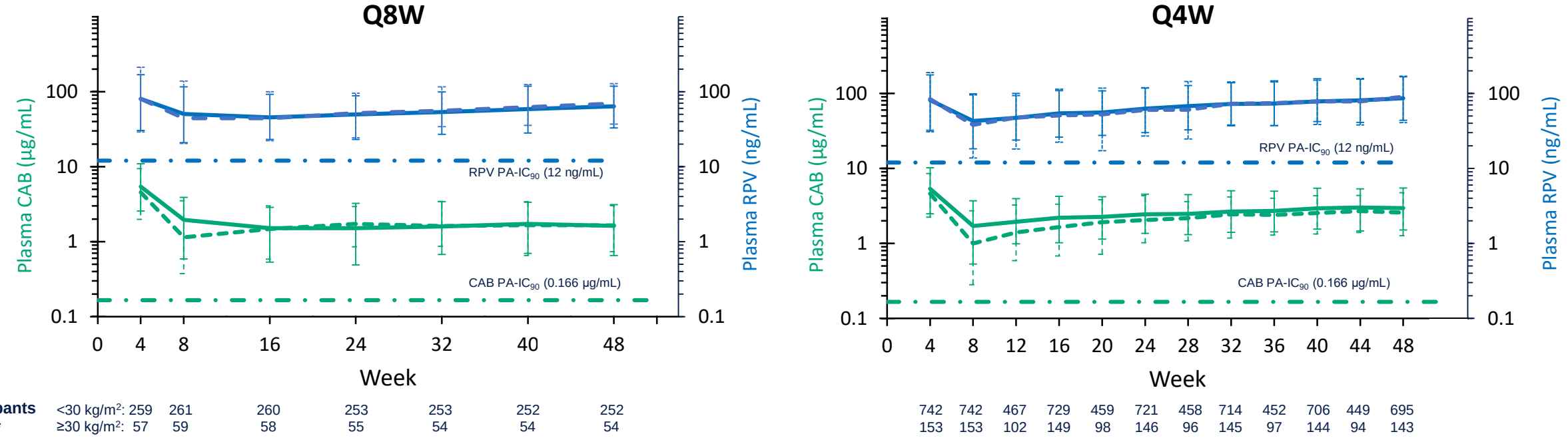
CAB and RPV Troughs Remained Above Respective PA-IC$_{90}$ Targets Regardless of Baseline BMI Category

Median (5th and 95th percentile) plasma CAB and RPV troughs through Week 48



Participants at visit*							
<30 kg/m^2:	259	261	260	253	253	252	252
≥30 kg/m^2:	57	59	58	55	54	54	54

Participants at visit*												
<30 kg/m^2:	742	742	467	729	459	721	458	714	452	706	449	695
≥30 kg/m^2:	153	153	102	149	98	146	96	145	97	144	94	143

BMI <30 kg/m^2 BMI ≥30 kg/m^2

- Median CAB troughs tended to be lower initially in participants with baseline BMI ≥30 kg/m^2, but this trend disappeared by Week 48
- RPV concentrations were unaffected by BMI category, consistent with previous findings[2]

*Participant numbers for CAB administration are shown. RPV participant numbers were identical with the following exceptions: Q8W, <30 kg/m^2: Week 16, n=259; Q8W, ≥30 kg/m^2: Week 4, n=58; Week 8, n= 58; Q4W, <30 kg/m^2: Week 8, n=743; Week 16, n= 730; Week 24, n=718; Week 32, n=715; Week 44, n=450; Week 48, n=691; Q4W, ≥30 kg/m^2: Week 4, n=152; Week 12, n=101; Week 24, n=147; Week 40, n=143; Week 48, n=144.
BMI, body mass index; CAB, cabotegravir; PA-IC$_{90}$, protein-adjusted 90% inhibitory concentration; Q4W, every 4 weeks; Q8W, every 8 weeks.
1. Cutrell AG, et al. *AIDS*. 2021;35(9):1333–1342. 2. Han K, et al. 22nd International AIDS Conference; Amsterdam, The Netherlands; July 23–27, 2018; poster WEPDB0205.

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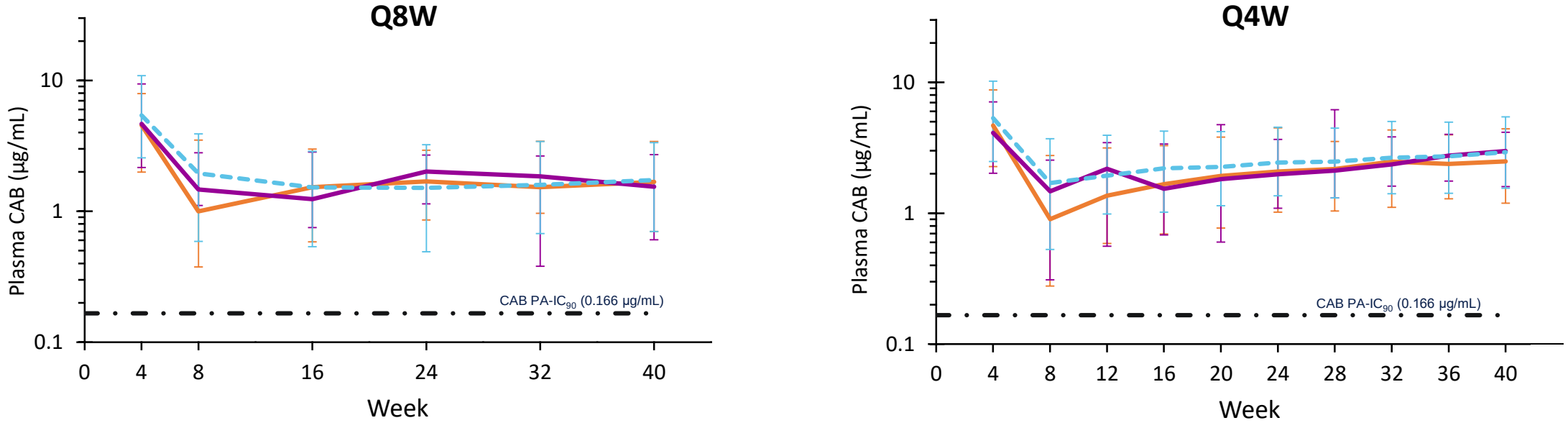
Longer Needle Lengths Were Associated With Higher CAB Troughs in the BMI ≥30 kg/m^2 Group Early in Treatment

Median (5th and 95th percentile)* plasma CAB troughs through Week 40 in participants with BMI ≥30 kg/m^2



Participants at visit*												
	49	51	49	47	45	45	130	131	88	122	83	122
	8	8	9	8	9	9	23	22	14	27	15	24
	259	261	260	253	253	252	742	742	467	729	459	721

80	118	82	120
16	27	15	24
458	714	452	706

<2 inches (BMI ≥30 kg/m^2) ≥2 inches (BMI ≥30 kg/m^2) BMI <30 kg/m^2 (reference)

- Use of longer 2-inch needles resulted in higher median CAB trough concentrations for participants with BMI ≥30 kg/m^2
- Longer 2-inch needles are recommended to accommodate individual body habitus and in participants with BMI ≥30 kg/m^2 to ensure appropriate administration into gluteal muscle†

*Data beyond Week 40 were not available at time of analysis.
†The majority (78%, n=3889/4970) of injections in participants with BMI ≥30 kg/m^2 were administered with needles <1.6 inches in length vs. the recommended longer 2-inch needle due to issues with procurement.
BMI, body mass index; CAB, cabotegravir; PA-IC$_{90}$, protein-adjusted 90% inhibitory concentration; Q4W, every 4 weeks; Q8W, every 8 weeks.

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Conclusions

- CAB + RPV LA Q4W and Q8W maintained high virologic suppression rates through Week 48 in Phase 3/3b trials, regardless of baseline BMI category
- Injections were well tolerated regardless of BMI category, rarely leading to study withdrawal; most ISRs were classified as mild to moderate in severity and decreased in incidence over time
- No participant with BMI ≥30 kg/m^2 as the only baseline risk factor met the CVF criterion through Week 48
- These data support the use of CAB + RPV LA dosed monthly or every 2 months as a complete regimen for the maintenance of HIV-1 virologic suppression in adults regardless of BMI category

BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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