CARISEL: A Hybrid Type III Implementation Effectiveness Study of Implementation of Cabotegravir + Rilpivirine Long-Acting (CAB + RPV LA) in European Health Care Settings; Key Clinical and Implementation Outcomes by Implementation Arm

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- Dr Czarnogorski is an employee of ViiV Healthcare and a stockholder of GSK
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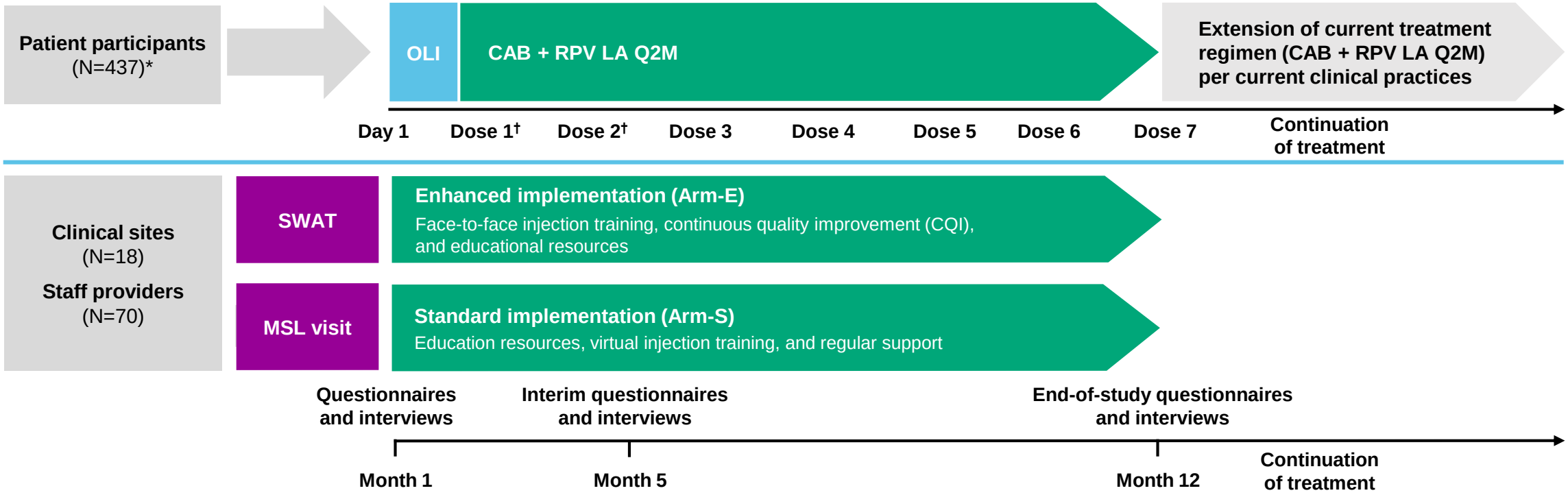
Introduction

- Cabotegravir + rilpivirine long-acting (CAB + RPV LA) dosed every 2 months (Q2M) is a recommended regimen in European and US treatment guidelines for virologically suppressed people living with HIV-1 (PLWH)[1,2]
- CAB + RPV LA reduces dosing frequency compared with daily oral antiretroviral therapy (ART), and may help address concerns including fear of disclosure, anxiety around medication adherence, and daily reminders of HIV status[3]
- CAB And RPV Implementation Study in European Locations (CARISEL*) is a Phase 3b, multicenter, open-label, hybrid type III implementation–effectiveness trial examining strategies to support the implementation of CAB + RPV LA dosed Q2M across five European countries
- In this presentation, we will present key clinical endpoints by implementation arm: Enhanced arm (Arm-E) and Standard arm (Arm-S)

*NCT04399551.
Arm-E, Enhanced Arm; Arm-S, Standard Arm; ART, antiretroviral therapy; CAB, cabotegravir; LA, long-acting; PLWH, people living with HIV-1; Q2M, every 2 months; RPV, rilpivirine.
1. European Medicines Agency. Vocabria. 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vocabria. Accessed September 2022. 2. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2021. Available from: https://clinicalinfo.hiv.gov/en/guidelines. Accessed September 2022. 3. De Los Rios P, et al. *Open Forum Infect Dis*. 2019;6(Suppl. 2):S481.

Study Design

CARISEL: Hybrid Type III Implementation–Effectiveness, Phase 3b, Open-Label Study Across Five European Countries



- 18 clinics across Belgium, France, Germany, the Netherlands, and Spain were randomized to implementation support packages: Enhanced Arm (Arm-E) and Standard Arm (Arm-S)
- Most (72%, n=13/18) clinics had no experience with CAB + RPV LA at study start

*437 patient participants enrolled, 430 received CAB + RPV LA. †Dose 1 was received at Month 1, Dose 2 at Month 2, with the remaining doses Q2M thereafter.
Arm-E, Enhanced Arm; Arm-S, Standard Arm; CAB, cabotegravir; CQI, continuous quality improvement; LA, long-acting; MSL, medical scientific liaison; OLI, oral lead-in; Q2M, every 2 months; RPV, rilpivirine; SWAT, skilled wrap-around team.

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Implementation Support

	Arm-E	Arm-S
Study treatment injection training (prior to first injection)	Face-to-face*	Virtual
Toolkits (patient/staff participant)	✓	✓
SWAT† meeting(s)	✓	
CQI‡ calls (monthly)	✓	

SWAT meetings:

- Introduce CAB + RPV LA to clinic staff and discuss what might make implementation easier, and/or what might make it difficult, prior to first injection at the site
- Meetings started to discuss an implementation plan, how to work through challenges, and introduce CQI

CQI:

- A process to support improving routine care by identifying problems, planning a solution, studying the results, and acting accordingly
- Process is documented through Plan, Do, Study, and Act cycles

*Four staff study participants in Arm-E received their injection training remotely rather then face-to-face due to COVID-19 restrictions. †Skilled wrap-around team (SWAT). ‡Continuous quality improvement (CQI).
Arm-E, Enhanced Arm; Arm-S, Standard Arm; CAB, cabotegravir; CQI, continuous quality improvement; LA, long-acting; RPV, rilpivirine; SWAT, skilled wrap-around team.

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Month 12 Endpoints (Overall and by Implementation Arm)

- The proportion of participants with plasma HIV-1 RNA ≥50 copies/mL and <50 copies/mL (FDA Snapshot algorithm)
- Incidence of confirmed virologic failure (CVF; two consecutive HIV-1 RNA measurements of ≥200 copies/mL) and suspected virologic failure (SVF; one HIV-1 RNA measurement of ≥200 copies/mL)
- Safety and tolerability
- COVID-19-related events

CVF, confirmed virologic failure; FDA, U.S. Food and Drug Administration; SVF, suspected virologic failure.

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Baseline Patient Characteristics

ITT-E population	CAB + RPV LA		
	Overall (N=430)	Arm-E (n=220)	Arm-S (n=210)
Median age (range), years	44 (37–51)	45 (36–52)	43 (38–51)
Age ≥50 years, n (%)	129 (30)	67 (30)	62 (30)
Female sex at birth, n (%)	109 (25)	57 (26)	52 (25)
Female self-reported gender, n (%)	115 (27)	61 (28)	54 (26)
Race, n (%)			
White	336 (78)	169 (77)	167 (80)
Black or African American	76 (18)	42 (19)	34 (16)
Asian	9 (2)	3 (1)	6 (3)
Other races*	9 (2)	6 (3)	3 (1)
Median BMI (IQR), kg/m^2	25 (23–28)	25 (23–28)	25 (23–27)

- Overall, 430 enrolled and treated participants were included
- Baseline characteristics were similar between arms, with 25% of participants being female (sex at birth), 18% being of Black or African American race, and 30% being aged ≥50 years

*American Indian or Alaska Native (Arm-E, n=4; Arm-S, n=3); multiple races (Arm-E only, n=2).
Arm-E, Enhanced Arm; Arm-S, Standard Arm; BMI, body mass index; CAB, cabotegravir; IQR, interquartile range; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.

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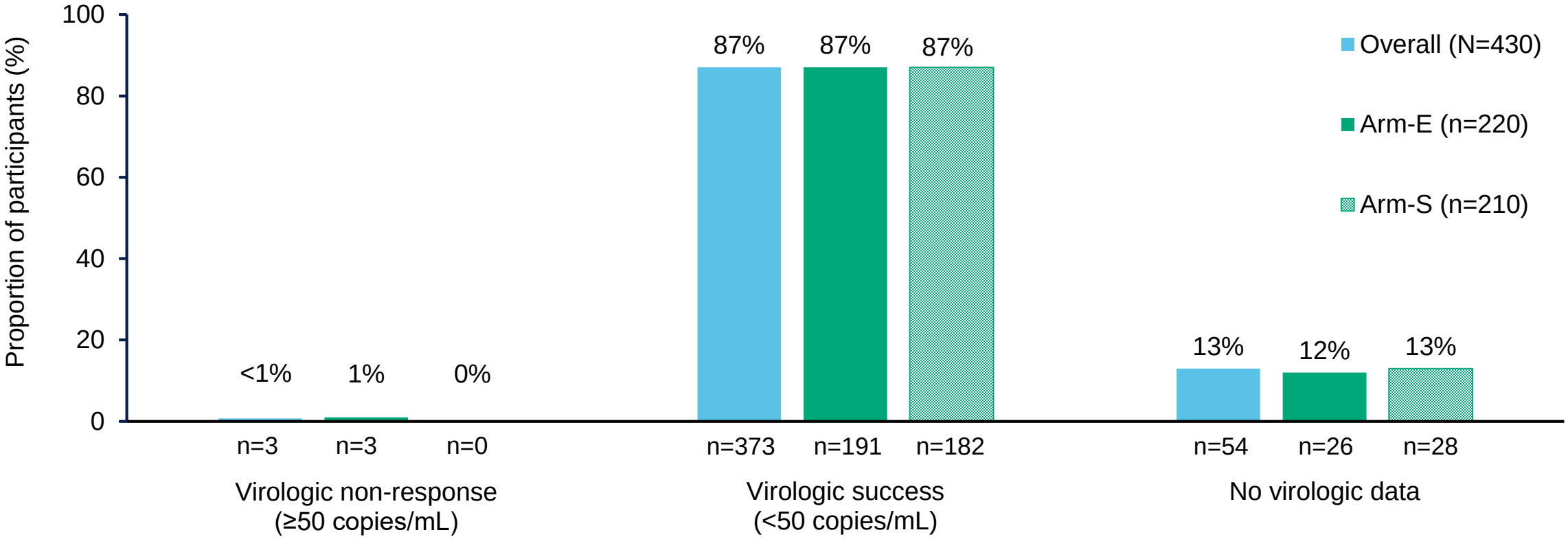
CAB + RPV LA Maintained High Levels of Virologic Suppression at Month 12 (Snapshot, ITT-E)



- At Month 12, 87% (95% CI 83.2–89.8) of participants maintained virologic suppression, with 0.7% (95% CI 0.1–2.0) having virologic non-response

Arm-E, Enhanced Arm; Arm-S, Standard Arm; CAB, cabotegravir; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.

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Snapshot Outcomes Were Similar Between Arms at Month 12 (Snapshot, ITT-E)

Parameter, n (%)	CAB + RPV LA		
	Overall (N=430)	Arm-E (n=220)	Arm-S (n=210)
HIV-1 RNA <50 copies/mL (Snapshot)	373 (87)	191 (87)	182 (87)
HIV-1 RNA ≥50 copies/mL (Snapshot)	3 (<1)	3 (1)	0
Data in window not below threshold	0	0	0
Discontinued for lack of efficacy	1 (<1)	1 (<1)	0
Discontinued for other reason while not below threshold*	2 (<1)	2 (<1)	0
No virologic data (Snapshot)	54 (13)	26 (12)	28 (13)
Discontinued study due to AE or death	40 (9)	20 (9)	20 (10)
Discontinued for other reason†	7 (2)	5 (2)	2 (<1)
On study but missing data in window‡	7 (2)	1 (<1)	6 (3)

- By Snapshot, 13% of participants had no virologic data available and 0.7% had HIV-1 RNA ≥50 copies/mL at Month 12

*Physician decision, n=2. †Protocol deviation, n=3; lost to follow-up, n=1; withdrawal by participant, n=3. ‡6 out of 7 participants at one site had a missed viral load assessment at Month 12 and had HIV-1 RNA <50 copies/mL at Month 14. The seventh participant from another site had HIV-1 RNA <50 copies/mL at last visit (Month 8) and transitioned to commercial CAB + RPV LA, following a missed central laboratory viral load assessment at Month 12 and a local Month 12 viral load of <20 copies/mL.
AE, adverse event; Arm-E, Enhanced Arm; Arm-S, Standard Arm; CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.

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One Participant Met the CVF Criterion and One Met the SVF Criterion*

Sex at birth, baseline BMI (kg/m²), country	HIV-1 subtype at baseline	Viral load at SVF/CVF (copies/mL)	RPV RAMs observed at baseline	INI RAMs observed at baseline	RPV RAMs observed at failure	INI RAMs observed at failure	Phenotypic resistance (fold-change) to RPV/CAB‡
Participant with CVF†							
Female, 29, Germany	G	214/1861	E138A	None	E138A + M230L	None	22.0/0.9
Participant with SVF§							
Male, 30, Spain	B	585/NA	None	None	E138K	N155N/S‖	6.1/1.3

- One participant (0.23%) in Arm-E experienced CVF through Month 12 with a viral load of 1861 copies/mL at discontinuation (Month 10)
  - In the CVF sample at Month 10, the RPV resistance-associated mutations (RAMs) E138A + M230L were detected; no integrase inhibitor (INI) RAMs were detected; E138A was present in baseline peripheral blood mononuclear cells (PBMCs)
- An additional participant in Arm-E met the SVF criterion twice at Month 4; neither were confirmed upon retest, and the participant withdrew following the second SVF§
  - The RPV RAM E138K and INI RAM N155N/S were detected in the SVF sample at Month 4; no INI or RPV RAMs were present in baseline PBMCs

*Data previously presented at IAS 2022, poster EPLBB05 "Safety and Effectiveness From the CARISEL Study: Phase 3b Hybrid-III Implementation Study Integrating Cabotegravir + Rilpivirine Long-Acting Into European Clinical Settings."
†Following discontinuation, the participant switched to darunavir/cobicistat/emtricitabine/tenofovir alafenamide. ‡The CVF and SVF virus was susceptible to CAB, dolutegravir, and bictegravir. §Participant met the SVF criterion (HIV-1 RNA 585 copies/mL) at Month 4 but was not confirmed at the Month 4 retest. Following a second retest at Month 4, the participant met the SVF criterion (HIV-1 RNA 386 copies/mL at timing of resistance test) and withdrew from the study, as per the principal investigator's discretion, and switched ART to darunavir/cobicistat/emtricitabine/tenofovir alafenamide. ‖N155S is an extremely rare, non-polymorphic mutation that reduces raltegravir and elvitegravir susceptibility to a lesser degree than N155H.[1]
1. Stanford University. HIV Drug Resistance Database. INSTI Resistance Notes. 2022. Available from: https://hivdb.stanford.edu/dr-summary/resistance-notes/INSTI/. Accessed August 2022.
Arm-E, Enhanced Arm; Arm-S, Standard Arm; ART, antiretroviral therapy; BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; RPV, rilpivirine; SVF, suspected virologic failure.

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Safety Profiles (Excluding Injection Site Reactions [ISRs]) Were Similar Between Arms Through Last Participant Last Visit*

Parameter, n (%)	CAB + RPV LA		
	Overall (N=430)	Arm-E (n=220)	Arm-S (n=210)
Any AE	363 (84)	190 (86)	173 (82)
Drug-related	156 (36)	81 (37)	75 (36)
Any Grade ≥3 AE	37 (9)	17 (8)	20 (10)
Drug-related	10 (2)	4 (2)	6 (3)
AEs leading to withdrawal	26 (6)	10 (5)	16 (8)
Drug-related†	21 (5)	8 (4)	13 (6)
Any serious AE	15 (3)	11 (5)	4 (2)
Drug-related‡	1 (<1)	1 (<1)	0

- Excluding ISRs, drug-related Grade ≥3 adverse events (AEs) occurred in 2% of participants, ranging 2–3% across implementation arms
- Excluding ISRs, drug-related withdrawals occurred in 4% and 6% of participants in Arm-E and Arm-S, respectively

*Month 14. †Weight gain, n=2; dizziness, n=1; myalgia, n=1; nausea, fever, and vomiting, n=1; non-cardiac chest pain, n=1; suicidal ideation, n=1; upper abdominal pain, abdominal distension, and diarrhea, n=1; abdominal distension and diarrhea, n=1; asthenia, insomnia, and irritability, n=1; decreased appetite, depressed mood, postural dizziness, headaches, malaise, and pain, n=1; depression, n=1; diarrhea, n=1; sciatica, n=1; asthenia and leg pain, n=1; anxiety, n=1; acute hepatitis, n=1; chills, fever, and night sweats, n=1; weight gain and lipodystrophy, n=1; insomnia, n=1; pain in right leg, chills, and fever, n=1. ‡Suicidal ideation, n=1.
AE, adverse event; Arm-E, Enhanced Arm; Arm-S, Standard Arm; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.

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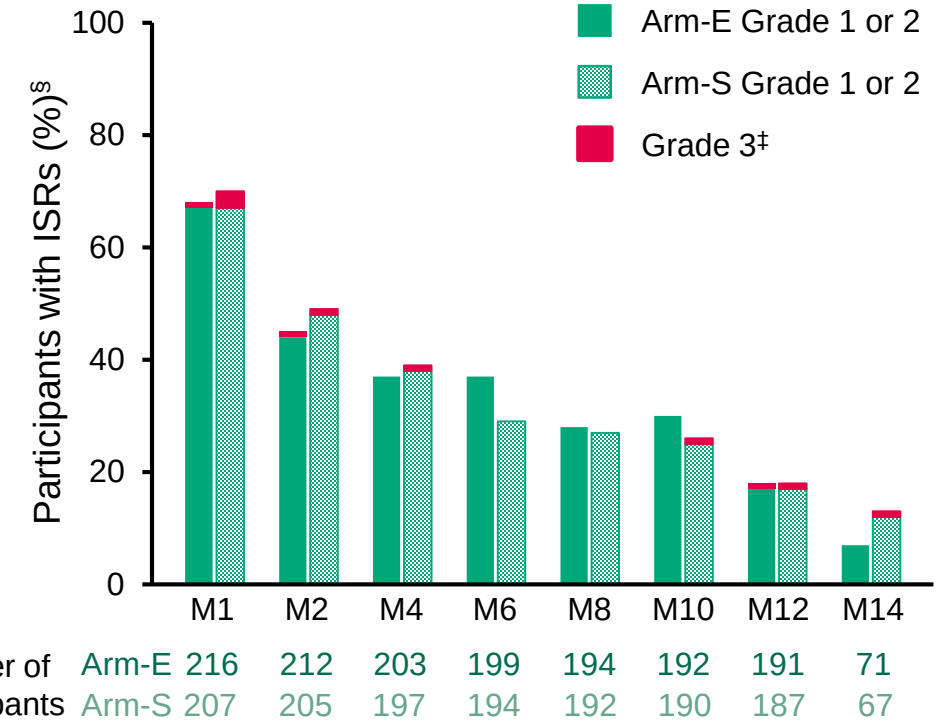
Most ISRs Were Grade 1 or 2, Short in Duration, and Decreased in Incidence Over Time

Parameter	CAB + RPV LA		
	Overall (N=430)	Arm-E (n=220)	Arm-S (n=210)
Participants who received ≥1 injection, n (%)	423 (98)	216 (98)	207 (99)
Number of injections, n	5844	2962	2882
ISR events, n*	1867	947	920
Pain, n (% of injections)†	1540 (26)	793 (27)	747 (26)
Discomfort, n (% of injections)†	94 (2)	54 (2)	40 (1)
Induration, n (% of injections)†	74 (1)	19 (<1)	55 (<2)
Grade 3, n (% of ISR events)‡	32 (2)	9 (<1)	23 (3)
Median duration (IQR), days	3 (2–5)	3 (2–5)	3 (2–6)
Participant withdrawal due to injection-related reasons, n (% of participants with injections)	25 (6)	16 (7)	9 (4)



- ISRs were reported in 86% of participants; 98% were mild or moderate in severity (most common event was pain)
- The median duration was 3 days, and a low proportion of participants (6%) withdrew for injection-related reasons
- The number of participants reporting ISRs at each visit decreased through Month 14

*Each ISR event was counted separately. A participant may have had multiple ISR events following a single injection. †ISRs occurring in over 1% of participants are listed. ‡There were no Grade 4 or 5 ISR events.
§AE grade is the maximum grade reported by the participant at each visit.
AE, adverse event; Arm-E, Enhanced Arm; Arm-S, Standard Arm; CAB, cabotegravir; IQR, interquartile range; ISR, injection site reaction; LA, long-acting; M, month; RPV, rilpivirine.

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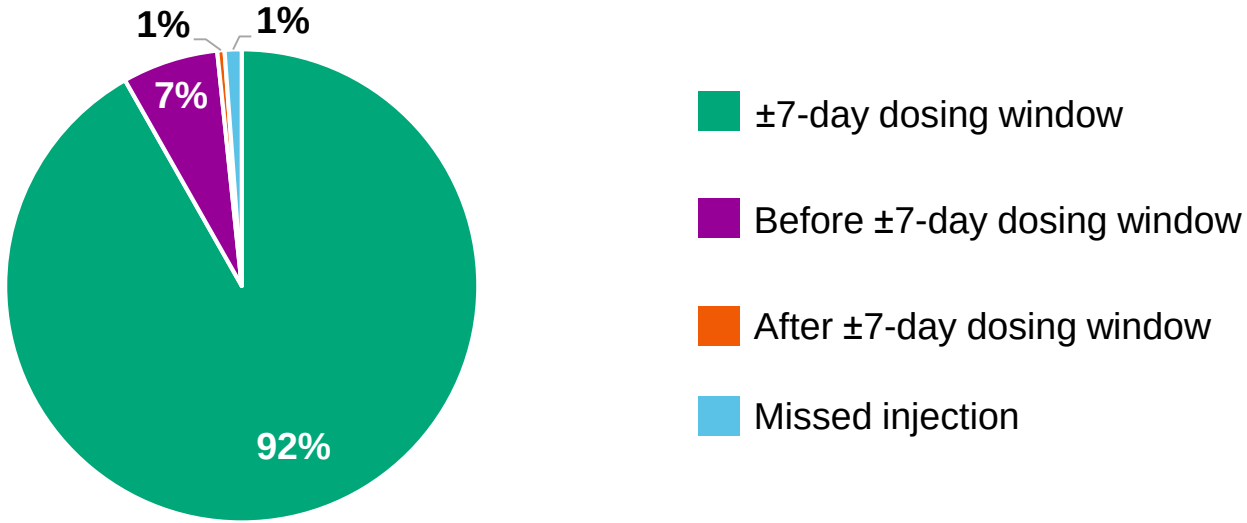
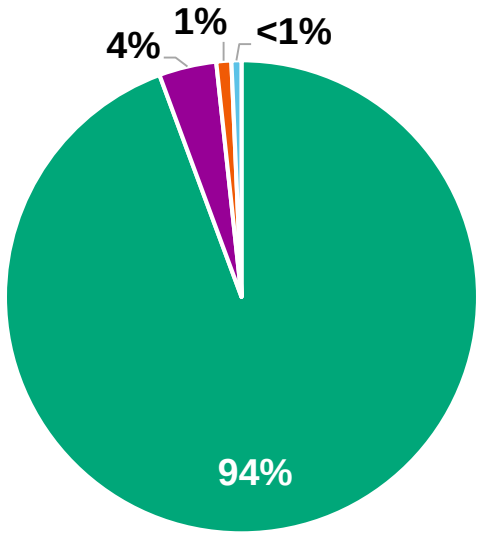
Rates of Adherence Were High Through Month 12

Arm-E (1205 injections)



Arm-S (1171 injections)



- Most injection visits occurred within the ±7-day dosing window
- Overall, 14 injection visits in Arm-E and eight injection visits in Arm-S were missed*

*Missed injections covered by oral ART: Arm-E, <1% (n=3/1205); Arm-S, <1% (n=3/1171). Missed injections with subsequent oral ART initiation: Arm-E, <1% (n=11/1205); Arm-S, <1% (n=5/1171).
Arm-E, enhanced arm; Arm-S, standard arm; ART, antiretroviral therapy.

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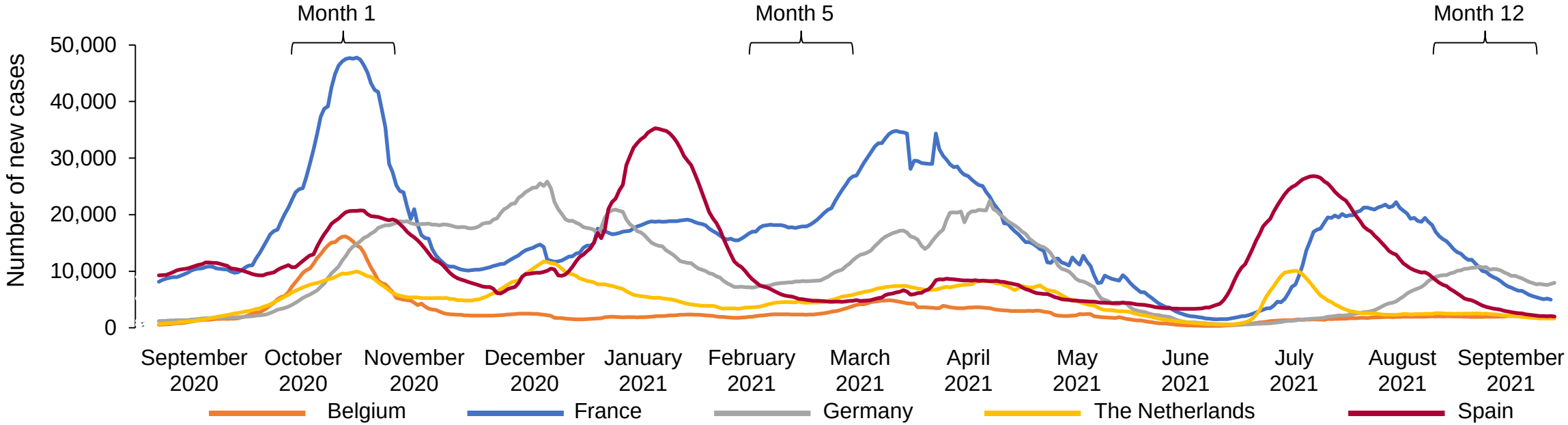
COVID-19 Pandemic Impact

Confirmed 7-Day Average Daily COVID-19 Cases in the Five European Countries During the CARISEL Study Period[1]



- Overall, COVID-19 was diagnosed in 16% of participants, and was similar by implementation arm
- COVID-19-related protocol deviations were reported in 3% of participants
- Five (<1%) participants received oral ART to cover a missed dose due to COVID-19
- There were no discontinuations or virologic non-response events due to COVID-19

1. WHO COVID-19 Dashboard. Geneva: World Health Organization. 2022. Available from: https://covid19.who.int. Accessed September 2022.

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Conclusions

- By design, the study enrolled a diverse population (gender, race, and age) representative of PLWH in Europe
- Key clinical outcomes were similar across both implementation arms, with 87% of participants maintaining HIV-1 virologic suppression, and 0.7% of participants having HIV-1 RNA ≥50 copies/mL by Snapshot algorithm at Month 12
  - This suggests that, regardless of implementation support and clinical infrastructure, CAB + RPV LA can be highly effective for a wide variety of PLWH
- CAB + RPV LA was well tolerated, with 98% of ISRs being Grade 1 or 2 and short-lived (median 3 days), with 6% of participants withdrawing due to injection-related reasons
- COVID-19 did not lead to treatment disruption or study discontinuation in either implementation arm

CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q2M, every 2 months; PLWH, people living with HIV-1; RPV, rilpivirine.

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