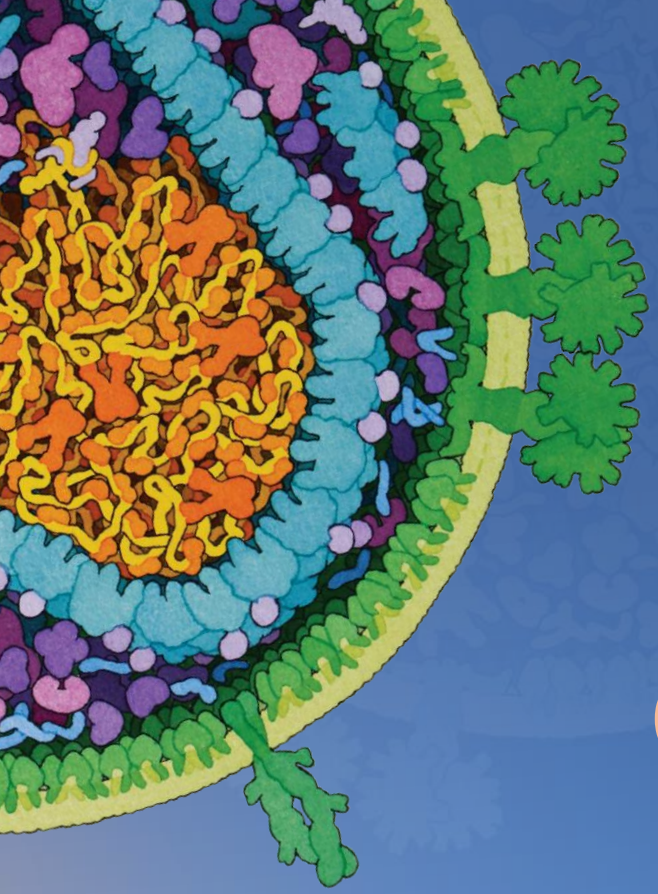


SCIENCE SPOTLIGHT™

WEEK 96 EFFICACY AND SAFETY OF LONG-ACTING CABOTEGRAVIR + RILPIVIRINE EVERY 2 MONTHS: ATLAS-2M

Hans Jaeger*, Edgar T. Overton, Gary Richmond, Giuliano Rizzardini, Jaime Federico Andrade-Villanueva, Rosie Mngqibisa, Antonio Ocampo Hermida, Anders Thalme, Paul D. Benn, Yuanyuan Wang, Krischan J. Hudson, David A. Margolis, Christine Talarico, Kati Vandermeulen, William R. Spreen

**MVZ Karlsplatz, HIV Research and Clinical Care Centre, Munich, Germany*

Disclosure: *Counselling, speaker's fees, and research support from ViiV Healthcare, Gilead, and MSD

CROI 2021

ATLAS-2M Week 96: Introduction

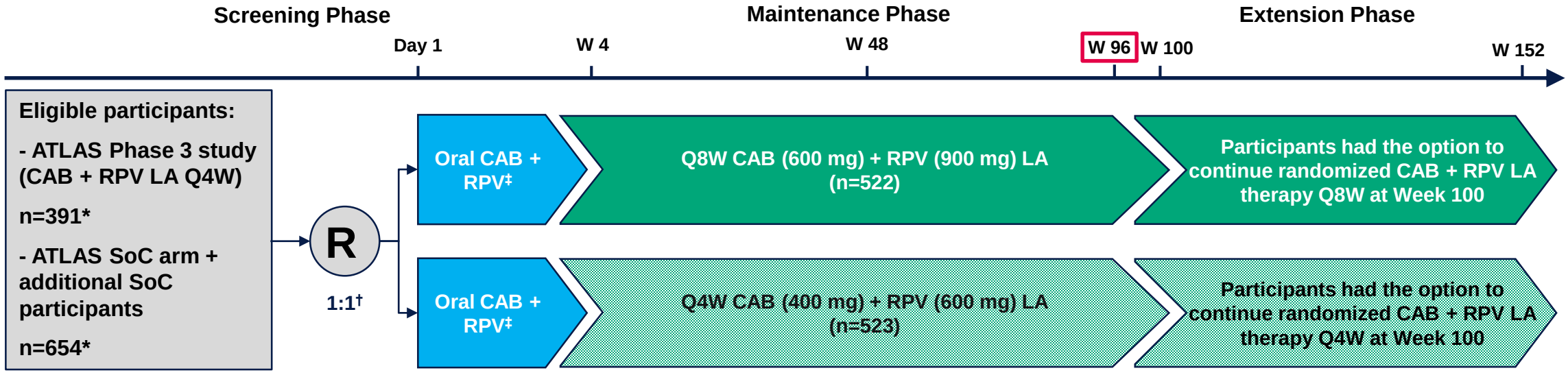
- Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI, have been approved in the US, Canada, and Europe as the first complete long-acting (LA) injectable regimen indicated for the maintenance of virologic suppression in people living with HIV-1[1–3]
- CAB + RPV LA administered monthly[4,5] or at a longer every 2 months dosing interval[6] may address challenges associated with daily oral ART, such as stigma, pill burden, drug/food interactions, and adherence
- Here, we report the Week 96 results of the ATLAS-2M study

ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

1. ViiV Healthcare. Cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension (Cabenuva) Prescribing Information. US, January 2021.
2. ViiV Healthcare. Vocabria Summary of Product Characteristics. EU, January 2020.
3. ViiV Healthcare. Vocabria (cabotegravir tablets) and Cabenuva (cabotegravir and rilpivirine extended release injectable suspensions) Product Monograph. Canada, March 2020.
4. Swindells S, et al. N Engl J Med. 2020;382(12):1112–1123.
5. Orkin C, et al. N Engl J Med. 2020;382(12):1124–1135.
6. Overton ET, et al. Lancet. 2020;396(10267):1994–2005.

ATLAS-2M Week 96: Study Design

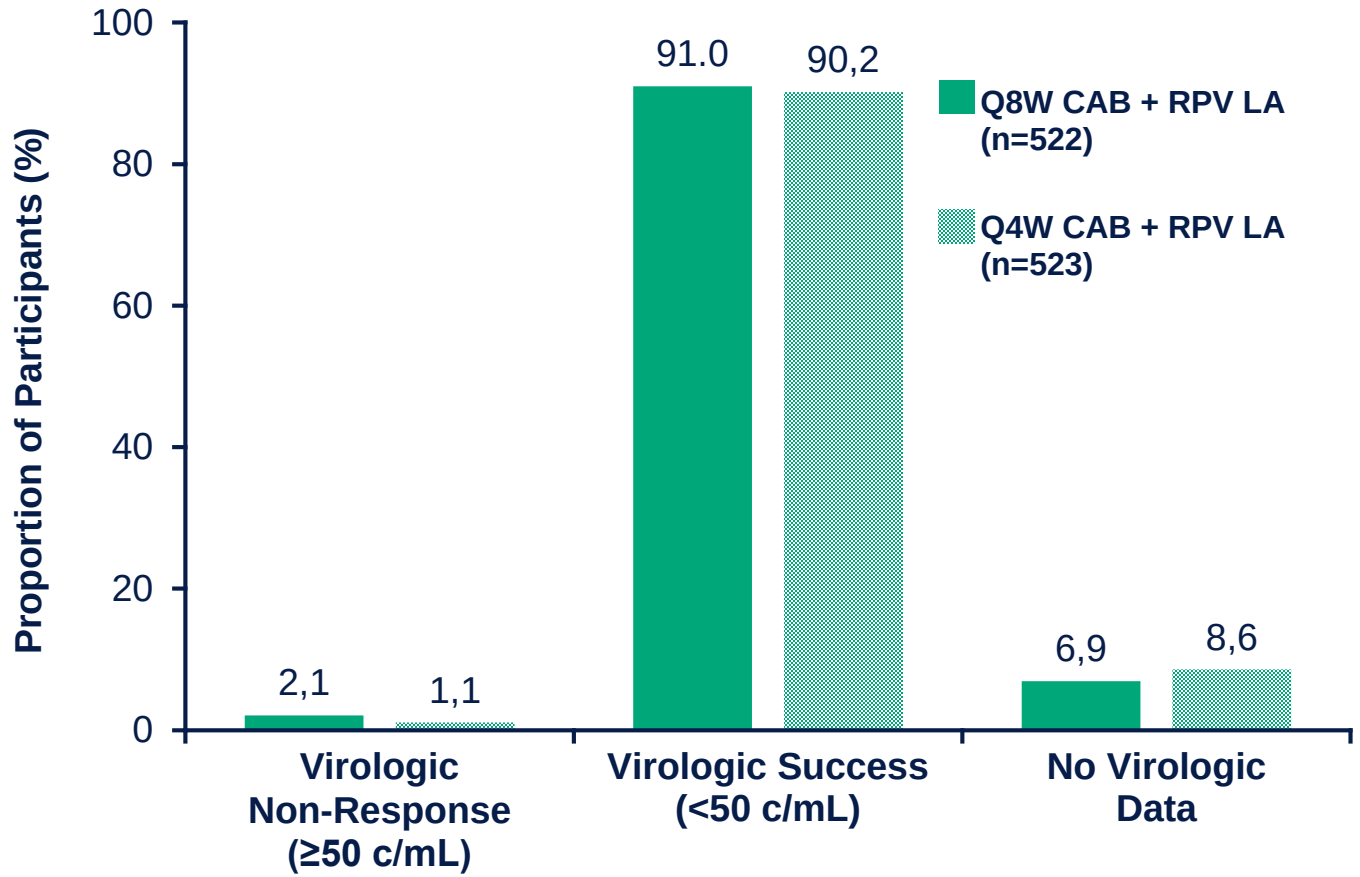
Phase 3b, randomized, multicenter, parallel-group, noninferiority, open-label study

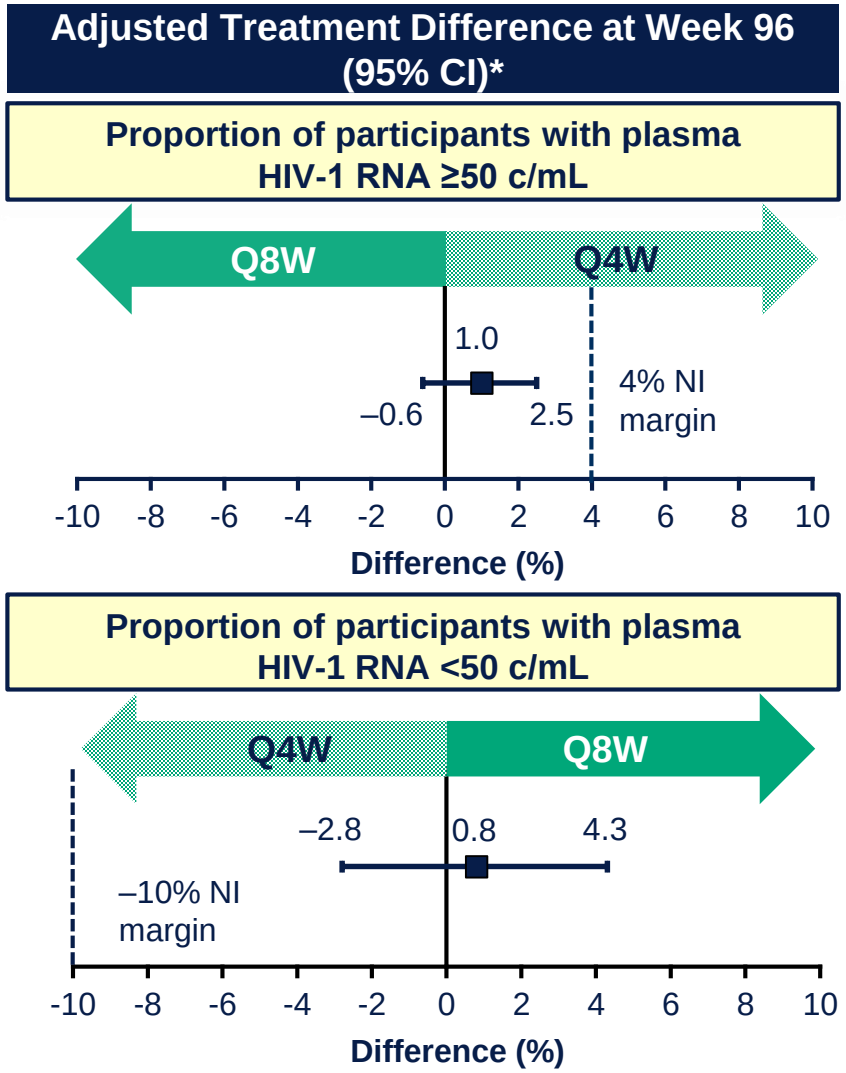


- The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E)
- Secondary endpoints included the proportion of participants with plasma HIV-1 RNA ≥50 or <50 c/mL at Week 96 (Snapshot, ITT-E)
- Other endpoints assessed at Week 96 included the incidence of CVF (two consecutive plasma HIV-1 RNA levels ≥200 c/mL), incidence of viral resistance in participants with CVF, and safety and tolerability

*ITT-E population. †Randomization was stratified by prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). ‡Excluding participants with prior CAB + RPV exposure in ATLAS.
For further study design details, please see Overton et al. CROI 2020; Boston, MA. Presentation 3334.[1]
CAB, cabotegravir; CVF, confirmed virologic failure; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomized; RPV, rilpivirine; SoC, standard of care; W, week.
Overton ET, et al. Conference on Retroviruses and Opportunistic Infections 2020; Boston, MA; March 8–11, 2020. Presentation 3334. Available from: www.croiwebcasts.org/p/2020croi/croi/34

ATLAS-2M Week 96: Virologic Snapshot Outcomes for ITT-E: CAB + RPV LA Continued to Maintain High Levels of Viral Suppression





*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).
CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

ATLAS-2M Week 96: Snapshot Outcomes at Week 96 (ITT-E Population)

	Q8W* (n=522)	Q4W* (n=523)
HIV-1 RNA <50 c/mL	475 (91.0)	472 (90.2)
Adjusted† difference (95% CI)	0.8 (–2.8, 4.3)	
HIV-1 RNA ≥50 c/mL	11 (2.1)	6 (1.1)
Adjusted† difference (95% CI)	1.0 (–0.6, 2.5)	
Data in window not below threshold	2 (0.4)	2 (0.4)
Discontinued for lack of efficacy	8 (1.5)	3 (0.6)
Discontinued for other reason while not below threshold	1 (0.2)	1 (0.2)
No virologic data	36 (6.9)	45 (8.6)
Discontinued study due to AE or death‡	17 (3.3)	17 (3.3)
Discontinued study for other reason	16 (3.1)	27 (5.2)
On study but missing data in window	3 (0.6)	1 (0.2)

*No discontinuations were attributed to COVID-19, though missing virologic data for four on-study participants were deemed to be COVID-19 related. COVID-19 introduced negligible impact on efficacy and no impact on the conclusions drawn at Week 96. n (%) unless otherwise stated
†Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks)
‡There were two deaths in the Maintenance Phase; one due to sepsis reported in the Week 48 analysis (Q8W arm), and one due to suicide since the Week 48 analysis (Q4W arm)
AE, adverse event; CI, confidence interval; ITT-E, intention-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

ATLAS-2M Week 96: One Participant Met the CVF Criterion Between Week 48 and 96

Overall Summary of CVFs through Week 96

	n	CVFs n (%)	CVFs with RPV RAMs*	RPV RAMs observed at failure	CVFs with IN RAMs*	IN RAMs observed at failure
Q8W	522	9 (1.7)	7/9	K101E, E138E/K, E138A, Y188L, Y181C	5/9	Q148R,† N155H†
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

- One additional participant, who was in the Q8W arm, met the CVF criterion between Week 48 and 96 (Week 88)‡
  - NNRTI RAM K103N and RPV RAM Y181C were detected at virologic failure in the plasma sample and retrospectively at baseline in the PBMC sample
  - No INSTI RAMs were present at virologic failure in the plasma sample or in the baseline PBMC sample; IN substitution L74L/I was present at baseline
- 10/11 CVFs resuppressed on alternative regimens (one participant was non-adherent to PI-based ART)
- All participants with CVF retained phenotypic susceptibility to dolutegravir

*For those with observed RAMs at failure: 7/7 Q8W and 1/1 Q4W CVFs had RPV resistance (fold-change >2), and 3/5 Q8W and 1/2 Q4W CVFs had CAB resistance (fold-change >2.5). †Or mixture.
‡The participant with CVF was a male from the US with a BMI <30 kg/m^2 and HIV-1 subtype B. The participant had a viral load of 1916 c/mL at SVF and 9063 c/mL at the confirmatory visit.
ART, antiretroviral therapy; BMI, body mass index; CVF, confirmed virologic failure; IN, integrase; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PBMC, peripheral blood mononuclear cell; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine; SVF, suspected virologic failure.

ATLAS-2M Week 96: Adverse Event Profiles and Injection Site Reactions Were Similar Between Q8W and Q4W Dosing

	Q8W (n=522) n (%) [delta*]	Q4W (n=523) n (%) [delta*]
Any AE	488 (93) [+15]	499 (95) [+17]
Drug-related AEs	415 (80) [+15]	413 (79) [+14]
Excluding ISRs	122 (23) [+13]	146 (28) [+21]
Any Grade ≥3 AE	57 (11) [+16]	65 (12) [+16]
Drug-related (excluding ISRs)†	8 (2) [+4]	10 (2) [+5]
Leading to withdrawal	18 (3) [+6]	19 (4) [+6]
Drug-related (excluding ISRs)	8 (2) [+3‡]	12 (2) [+4§]
Any serious AE	33 (6) [+6]	28 (5) [+9]
Drug-related (excluding ISRs)	3 (<1) [+1‖]	3 (<1) [+2¶]

	Q8W (n=522) n (%)	Q4W (n=523) n (%)
Number of injections	12,832	23,855
ISR events	3400	4157
Injection site pain**	2662 (21)	3295 (14)
Injection site nodule**	188 (1)	297 (1)
Injection site discomfort**	134 (1)	148 (<1)
Grade 3††	54	50
Median duration, days (IQR)	3 (2, 5)	3 (2, 5)
Participants withdrawing for injection-related reasons, n (%)	7 (1)	11 (2)

- The AE profile remained consistent through the Week 48 and Week 96 analyses
- The type and frequency of AEs were similar between arms; the most common non-ISR drug-related AEs were pyrexia and fatigue
- Most ISRs were Grade 1–2 (99%, n=7453/7557), with <2% of participants withdrawing due to injection-related reasons; only one participant (Q8W arm) withdrew since the Week 48 analysis
- The number of participants experiencing an ISR at each visit decreased over the duration of the study‡‡

*Delta value represents new participants with AEs since the Week 48 analysis. †One drug-related AE in each arm was Grade 4; none were Grade 5. ‡Malaise and hyperhidrosis (n=1), headache (n=1), osteonecrosis (n=1). §Disturbance in attention and sleep disorder (n=1), nausea and vertigo (n=1), drug hypersensitivity (n=1), myocardial infarction (n=1). ‖Osteonecrosis (n=1). ¶Drug hypersensitivity (n=1) and myocardial infarction (n=1). **Percentages are calculated from the total number of injections. Those occurring with ≥1% of injections in either treatment arm are shown. ††There were no Grade 4 or Grade 5 ISRs. ‡‡Week 48: Q8W, n=115/493 (23%); Q4W, n=100/488 (20%); Week 96: Q8W, n=74/473 (16%); Q4W, n=54/468 (12%). AE, adverse event; IQR, interquartile range; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks.

ATLAS-2M Week 96: Conclusions

- Both dosing regimens of CAB + RPV LA maintained high levels of virologic suppression (Q8W 91%; Q4W 90%), with few participants having HIV-1 RNA ≥50 c/mL (Q8W, 2%; Q4W, 1%) at Week 96, demonstrating noninferiority of Q8W vs. Q4W dosing
  - The rate of CVF was low overall (n=11/1045 [1%]), with only one participant (Q8W arm) meeting the criterion in the second year of therapy
- CAB + RPV LA was well tolerated with a comparable safety profile between arms
  - No new safety signals were identified since the Week 48 analysis
  - ISRs were mostly Grade 1–2 (99%), short lived (median 3 days), and decreased in incidence over time
- These longer-term efficacy, safety, and tolerability data support CAB + RPV LA dosed monthly or Q2M as a complete regimen for the maintenance of HIV-1 virologic suppression in adults*

*Monthly dosing of CAB + RPV LA approved by the FDA (January 2021).
CAB, cabotegravir; CVF, confirmed virologic failure; FDA, U.S. Food and Drug Administration; ISR, injection site reaction; LA, long-acting; Q2M, every 2 months; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

ATLAS-2M Week 96: Acknowledgments

- The authors thank everyone who has contributed to the success of ATLAS-2M
  - All study participants and their families
  - The ATLAS-2M clinical investigators and their staff in Australia, Argentina, Canada, France, Germany, Italy, Mexico, Republic of Korea, Russian Federation, South Africa, Spain, Sweden, and the United States
  - ATLAS-2M was funded by ViiV Healthcare and Janssen Pharmaceuticals

Argentina
Cahn
Cassetti
Lupo
Porteiro

Australia
Baker
Bloch
Roth
Shields

Canada
Angel
Baril
Smith
Trottier
Wong
de Pokomandy

France
Ajana
Delobel
Girard
Katlama
Khuong-Josses
Molina
Reynes
Yazdanpanah

Germany
Arasteh
Baumgarten
Degen
Esser
Jaeger
Lutz
Rockstroh
Stellbrink
Stephan
Stoll

Italy
Castelli
Rizzardini

Mexico
Andrade-Villanueva

Republic of Korea
Choi
Kim S-W
Kim S-I
Kim Y
Lee

Russian Federation
Belonosova
Borodkina
Chernova
Gusev
Kulagin
Nagimova
Pokrovsky
Shuldyakov
Tonkikh
Tsybakova
Volkova
Voronin
Yakovlev

South Africa
Hoosen
Latiff
Lombaard
Mitha
Mngqibisa
Orrell
Petrick

Spain
Antela López
Castaño Carracedo
Falcó Ferrer
García Deltoro
Knobel Freud
Mallolas Masferrer
Masiá Canuto
Montes Ramírez
Moreno Guillén
Negredo Puigmal
Ocampo Hermida
Pulido Ortega
Rivero Román
Viciana Fernández

Sweden
Gisslén
Thalme
Treutiger

United States
Aberg
Bettacchi
Bredeek
Brennan
Brinson
Crofoot
Cunningham
Daar
De Vente
Felizarta
Fichtenbaum
Goldstein
Hare
Henry
Hoffman-Terry
Hsiao
Katner
Kumar
Lichtenstein
Luetkemeyer
McDonald
Mills
Newman
Olivet
Overton
Pierone
Polk
Presti
Ramgopal
Richmond
Ruane
Scarsella
Schreibman
Scott
Scribner
Simon
Sims
Swindells
Taiwo
Towner
Wheeler
Wohl

Editorial assistance was provided by Daniel Williams of SciMentum, with funding provided by ViiV Healthcare. Krischan J. Hudson and David A. Margolis were employed at ViiV Healthcare during the study but no longer work for the company