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MAJOR ARTICLE

Efficacy, Safety, and Durability of Long-Acting Cabotegravir and Rilpivirine in Adults With Human Immunodeficiency Virus Type 1 Infection: 5-Year Results From the LATTE-2 Study

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Background. In the Long-Acting Antiretroviral Treatment Enabling Trial 2 (LATTE-2) phase 2b study, long-acting (LA) injectable cabotegravir + rilpivirine dosed every 8 weeks (Q8W) or every 4 weeks (Q4W) demonstrated comparable efficacy with daily oral antiretroviral therapy (ART) through 96 weeks in ART-naive adults with human immunodeficiency virus type 1 (HIV-1). Here we report efficacy, tolerability, and safety of cabotegravir + rilpivirine LA over approximately 5 years.

Methods. After 20 weeks of oral cabotegravir + abacavir/lamivudine, participants were randomized to cabotegravir + rilpivirine LA Q8W or Q4W or continue oral ART through the 96-week maintenance period. In the extension period through week 256, participants continued their current LA regimen (randomized Q8W/Q4W groups) or switched from oral ART to Q8W or Q4W LA therapy (extension-switch groups). Endpoints assessed included proportion of participants with HIV-1 RNA <50 copies/mL (Snapshot algorithm) and adverse events (AEs).

Results. At week 256, 186 of 230 (81%) participants in randomized Q8W/Q4W groups and 41 of 44 (93%) participants in extension-switch groups had HIV-1 RNA <50 copies/mL. No protocol-defined virologic failures occurred after week 48. Injection wsite reactions infrequently resulted in discontinuation (4 [2%] and 1 [2%] participants in randomized Q8W/Q4W and extension-switch groups, respectively). Three participants in randomized Q8W/Q4W groups experienced drug-related serious AEs, including 1 fatal serious AE (Q4W group); none occurred in extension-switch groups. Of 25 participants with AEs leading to withdrawal, 20 were in the randomized Q4W group; no AE leading to withdrawal occurred in >1 participant.

Conclusions. Cabotegravir + rilpivirine LA exhibited long-term efficacy and tolerability, demonstrating its durability as maintenance therapy for HIV-1 infection.

Clinical Trials Registration. NCT02120352.

Keywords. cabotegravir; integrase strand transfer inhibitor; long-acting; nonnucleoside reverse transcriptase inhibitor; rilpivirine.

Although advances in antiretroviral therapy (ART) have made human immunodeficiency virus type 1 (HIV-1) infection a manageable condition, challenges with daily oral therapy, such as pill burden and stigma, may reduce treatment effectiveness and quality of life [1–4]. Long-acting (LA) injectable ART may address these challenges by eliminating daily oral dosing [5].

The first complete LA injectable regimen for HIV-1 treatment consists of cabotegravir, an integrase strand transfer inhibitor, and rilpivirine, a nonnucleoside reverse transcriptase inhibitor [6, 7]. The LATTE phase 2b study demonstrated that 72 weeks of oral cabotegravir + rilpivirine had similar efficacy

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to 3-drug oral ART and established oral lead-in doses for subsequent LA studies [8]. The LATTE-2 phase 2b study first evaluated efficacy and safety of an LA intramuscular injectable ART regimen in treatment-naive individuals with HIV-1 infection, demonstrating that cabotegravir + rilpivirine LA every 4 weeks (Q4W) or every 8 weeks (Q8W) had comparable efficacy to daily oral ART in maintaining HIV-1 suppression at 32, 48, and 96 weeks [9]. Cabotegravir + rilpivirine LA was generally well tolerated, and participants in LA groups reported high levels of treatment satisfaction [9, 10].

In the phase 3 studies Antiretroviral Therapy as Long Acting Suppression (ATLAS) and First Long-Acting Injectable Regimen (FLAIR), 48 weeks of cabotegravir + rilpivirine LA dosed intramuscularly Q4W was noninferior to daily oral ART for maintaining virologic suppression in adults with HIV-1 infection [11, 12]. Longer-term data in FLAIR demonstrated that cabotegravir + rilpivirine LA remained noninferior to daily oral ART at week 96 [13]. Based on these results, cabotegravir + rilpivirine LA dosed monthly has been approved in the United States, Canada, Europe, and Australia for maintenance of virologic suppression in adults [14–21]. Recently, cabotegravir + rilpivirine LA administered Q8W for 48 weeks demonstrated noninferior efficacy to Q4W dosing in the phase 3b ATLAS-2M study [22], resulting in simultaneous approval of every-2-months dosing in Europe and Australia [18–21].

Chronic use of LA injectables has not been evaluated for HIV-1 treatment, although its use has been well established for contraception and treatment of certain psychiatric disorders [23]. Patient acceptance and tolerance of receiving cabotegravir + rilpivirine LA for >2 years have not been evaluated [13]. Therefore, we report long-term efficacy, safety, and tolerability of cabotegravir + rilpivirine LA dosed Q4W and Q8W over approximately 5 years in LATTE-2.

METHODS

Study Design and Participants

LATTE-2 is a phase 2b, randomized, multicenter, parallel-group, open-label study using an induction-maintenance design conducted at 50 sites in Canada, France, Germany, Spain, and the United States (NCT02120352). Eligible participants were adults aged ≥18 years with HIV-1 RNA ≥1000 copies/mL, $CD4^+$ count ≥200 cells/μL, and ≤10 days of previous ART. Key exclusion criteria were presence of any major resistance-associated mutation, moderate/severe hepatic impairment, clinically relevant hepatitis, chronic hepatitis B infection, history of liver cirrhosis, creatinine clearance <50 mL/minute, laboratory values or electrocardiographic findings of clinical concern, long-term anticoagulation, and presence of HLA-B*5701 plus inability to use an abacavir-containing nucleoside reverse transcriptase inhibitor backbone.

During the induction period, eligible participants received once-daily oral cabotegravir 30 mg + abacavir 600 mg/lamivudine 300 mg for 20 weeks, with once-daily oral rilpivirine 25 mg added for the last 4 weeks (Figure 1A). Participants achieving HIV-1 RNA <50 copies/mL at week −4 who tolerated the regimen were randomized to receive intramuscular injections Q8W (cabotegravir 600 mg + rilpivirine 900 mg LA) or Q4W (cabotegravir 400 mg + rilpivirine 600 mg LA) or continue once-daily oral cabotegravir + abacavir/lamivudine in the 96-week maintenance period. Injections were scheduled with a ±7-day dosing window from the projected dosing date relative to the first injection on day 1. After week 96, participants randomized to LA therapy continued their maintenance period regimen into the extension period. Participants randomized to oral therapy could switch to their choice of LA dosing groups, either Q8W (cabotegravir 600 mg + rilpivirine 900 mg LA) or Q4W (cabotegravir 400 mg + rilpivirine 600 mg LA), in the extension period, starting with an optimized loading dose of cabotegravir 600 mg + rilpivirine 900 mg LA at week 100 and continuing to receive LA therapy for 156 weeks through week 256. Daily oral cabotegravir 30 mg + rilpivirine 25 mg was available for short-term temporary oral therapy in exceptional circumstances to cover planned interruptions in injection dosing with medical monitor approval.

Patient Consent Statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol was approved by investigational center ethics committees or institutional review boards of each study site. All participants provided written informed consent.

Study Endpoints and Assessments

Primary endpoints were proportion of participants in the intention-to-treat, maintenance-exposed population with HIV-1 RNA <50 copies/mL at week 32 using the US Food and Drug Administration Snapshot algorithm, proportion of participants with protocol-defined virologic failure (PDVF), and incidence and severity of adverse events (AEs) and laboratory abnormalities. Secondary endpoints included proportion of participants with HIV-1 RNA <50 copies/mL and changes from baseline in $CD4^+$ cell count over time. Adherence to the dosing window around injection visits was also assessed.

Plasma HIV-1 RNA was quantified using the Abbott RealTime HIV-1 assay (Abbott Molecular, Des Plaines, Illinois). Protocol-defined virologic failure was characterized as having 2 consecutive HIV-1 RNA measurements ≥200 copies/mL. Safety and tolerability were assessed by monitoring AEs, including injection site reactions (ISRs), laboratory assessments, vital signs, and electrocardiograms.

The intention-to-treat, maintenance-exposed population consisted of participants initially randomized to and receiving ≥1 dose of LA therapy during the maintenance period. The extension-switch population included

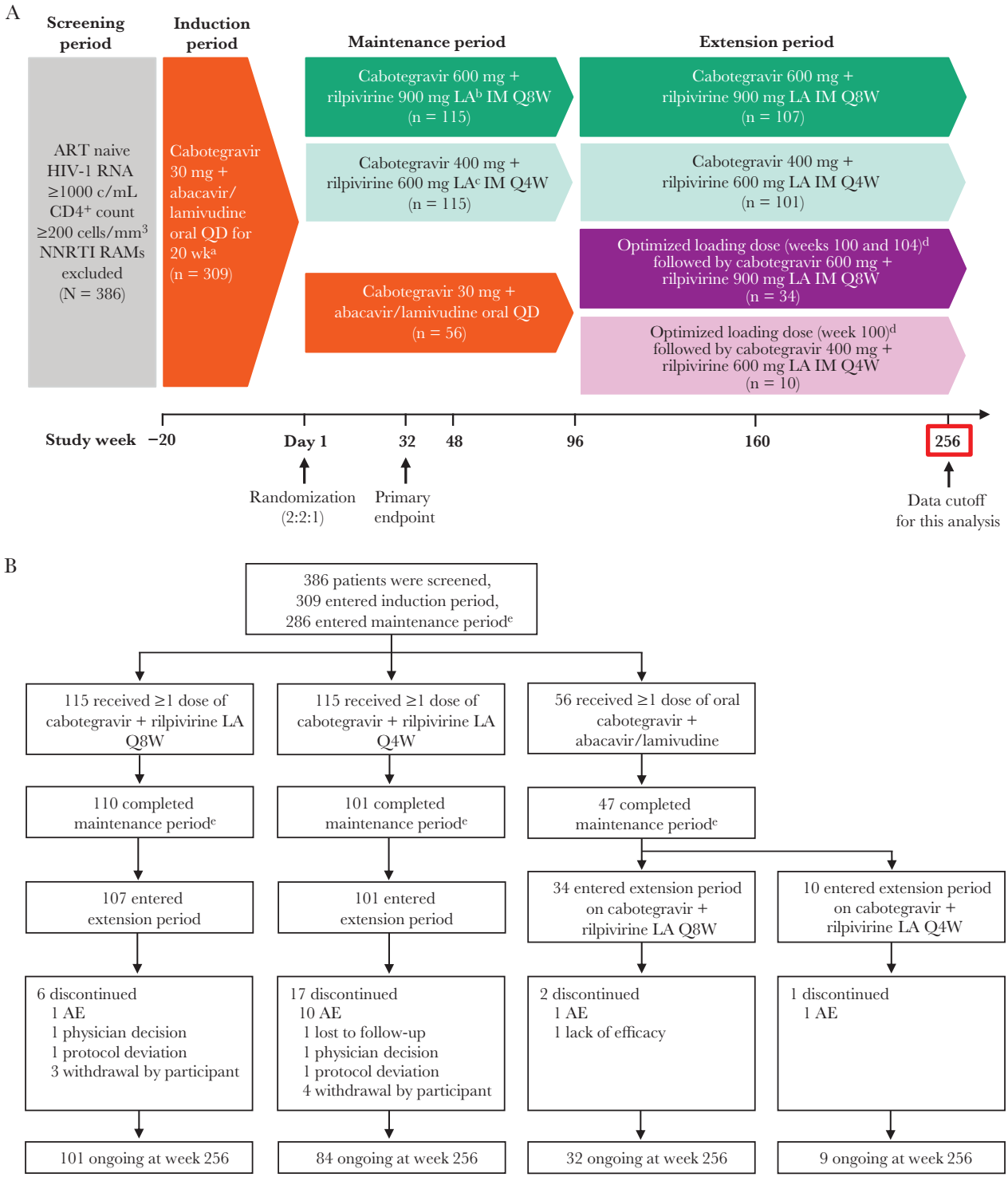

Figure 1. Study design (*A*) and participant disposition through week 256 (*B*). [a]Oral rilpivirine 25 mg once daily was added from week –4 to day 1. [b]Participants received a loading dose of cabotegravir 800 mg (two 2-mL injections) + rilpivirine 900 mg (one 3-mL injection) LA on day 1 and a second loading dose of cabotegravir 600 mg (one 3-mL injection) LA at week 4 before starting every-8-week dosing at week 8. [c]Participants received a loading dose of cabotegravir 800 mg (two 2-mL injections) + rilpivirine 600 mg (one 2-mL injection) LA on day 1 and started every-4-week dosing at week 4. [d]Optimized loading doses were cabotegravir 600 mg (one 3-mL injection) + rilpivirine 900 mg (one 3-mL injection) LA. [e]Reasons for discontinuation have been previously reported [9]. Abbreviations: AE, adverse event; ART, antiretroviral therapy; c/mL, copies per milliliter; HIV-1, human immunodeficiency virus type 1; IM, intramuscular; LA, long acting; NNRTI, nonnucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; RAM, resistance-associated mutation.

participants randomized to oral therapy during the maintenance period who switched to and received ≥1 dose of the optimized LA regimen in the extension period. Data are reported from the maintenance plus extension periods for the randomized Q8W/Q4W groups and from the extension period only for the extension-switch groups.

RESULTS

Study Population

The first participant was screened on 28 April 2014, and the last participant's week 256 visit occurred on 5 December 2019. Baseline characteristics were balanced among participants in the randomized Q8W/Q4W and extension-switch groups (Table 1).

Of 230 participants in the randomized Q8W/Q4W groups, 90% entered the extension period, and 80% were ongoing at week 256 (Figure 1B). In the extension period, 6 and 17 participants in the randomized Q8W and Q4W groups, respectively, withdrew; 11 participants (5%) withdrew because of AEs, 10 of whom were in the randomized Q4W group. Of 44 participants who switched to LA therapy in the extension period, 93% were ongoing at week 256. Three participants in the extension-switch groups withdrew, with 2 (5%; 1 from each group) withdrawing because of AEs.

Efficacy

At week 256, 88% (n = 101) and 74% (n = 85) of participants in the randomized Q8W and Q4W groups, respectively, maintained HIV-1 RNA <50 copies/mL (Figure 2; Table 2). After 156 weeks of LA therapy in the extension period, 94% (n = 32) and 90% (n = 9) of participants in the extension-switch Q8W and Q4W groups, respectively, maintained virologic suppression. Five participants had HIV-1 RNA ≥50 copies/mL at week 256 (n = 4 in the randomized Q8W group, n = 1 in the extension-switch Q8W group). A higher proportion of participants had no virologic data in the assessment window at week 256 in the randomized Q4W group (26%) vs the randomized Q8W group (9%), driven by more discontinuations due to AEs (n = 15) or death (n = 3) and other nonvirologic reasons, including participant withdrawal (n = 6), protocol deviation (n = 3), loss to follow-up (n = 1), and physician decision (n = 1) in the randomized Q4W group. One participant from each extension-switch group had no virologic data at week 256, both of whom discontinued due to AEs before week 256.

No participant in any group met PDVF criteria after week 48. Three participants (Q8W group, n = 2; oral treatment group, n = 1) met PDVF criteria through week 48 (Supplementary Materials) [9].

At week 256, mean $CD4^+$ cell counts increased from week −20 by 326 (standard deviation [SD], 218) cells/μL in the randomized Q8W group (n = 102) and 396 (SD, 294) cells/μL in the randomized Q4W group (n = 85). Mean $CD4^+$ cell count from week 100 to week 256 increased by 211 (SD, 318) cells/μL in the extension-switch Q4W group (n = 9) and decreased by 14 (SD, 319) cells/μL in the extension-switch Q8W group (n = 32).

Table 1. Baseline Demographics

	ITT, Maintenance-Exposed, Randomized Population		Extension-Switch Population	
	Q8W IM	Q4W IM	Q8W IM	Q4W IM
Characteristic	(n = 115)	(n = 115)	(n = 34)	(n = 10)
Age, y, median (range)	34 (20–64)	36 (19–62)	36 (19–56)	41 (21–56)
Reported gender, No. (%)				
Female	8 (7)	6 (5)	6 (18)	2 (20)
Male	107 (93)	109 (95)	28 (82)	8 (80)
BMI, kg/m^2, median (range)	24 (19–35)	24 (17–37)	24 (20–62)	24 (19–30)
Race, No. (%)				
White	93 (81)	94 (82)	24 (71)	6 (60)
Black/African American	17 (15)	12 (10)	10 (29)	3 (30)
American Indian/Alaska Native	0	8 (7)	0	1 (10)
Other	5 (4)	1 (<1)	0	0
Baseline $CD4^+$ cell count, cells/μL, median (IQR)	449 (343–618)[a]	499 (359–624)[a]	988 (747–1093)[b]	754 (644–962)[b]
Baseline HIV-1 RNA, log_{10} copies/mL, median (IQR)	4.42 (4.05–4.80)[a]	4.46 (4.00–4.97)[a]	1.59 (1.59–1.59)[b,c]	1.59 (1.59–1.59)[b,c]

Abbreviations: BMI, body mass index; HIV-1, human immunodeficiency virus type 1; IM, intramuscular; IQR, interquartile range; ITT, intention to treat; Q4W, every 4 weeks; Q8W, every 8 weeks.

[a]Baseline is at week −20.

[b]Extension baseline is at week 100.

[c]All participants had HIV-1 RNA <50 copies/mL at extension baseline.

Adherence

In the randomized Q8W/Q4W groups, 96% of 9803 expected injection visits through week 256 occurred within the ±7-day dosing window (Supplementary Figure 1). Through week 256, 208 (90%) participants demonstrated ≥90% adherence to injection visits within the ±7-day dosing window; 125 (54%) were 100% adherent. Of 23 (<1%) missed injection visits, 20 were planned interruptions in injection dosing and covered with oral cabotegravir + rilpivirine therapy between injection visits; temporary oral therapy was used for 3 injection visits in the Q8W group (n = 2) and 17 in the Q4W group (n = 6). Two participants in the Q4W group had ≥2 injection visits covered by oral dosing because of travel or prolonged psychiatric hospitalization. All participants who used temporary oral dosing to manage planned interruptions in injection dosing maintained

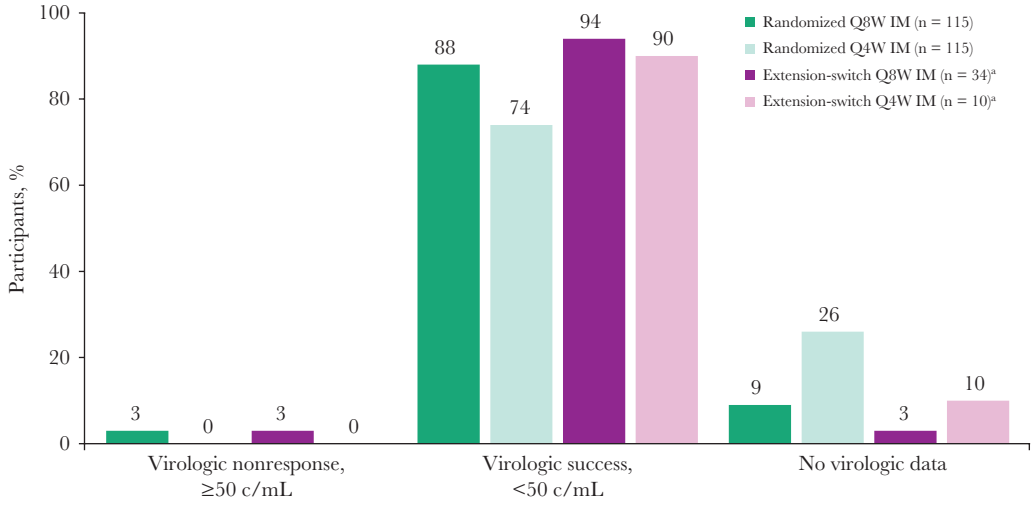

Figure 2. Virologic outcomes at week 256 by United States Food and Drug Administration Snapshot algorithm. [a]Participants in extension-switch groups switched to cabotegravir + rilpivirine long-acting at week 100. Abbreviations: c/mL, copies per milliliter; IM, intramuscular; Q4W, every 4 weeks; Q8W, every 8 weeks.

HIV-1 RNA <50 copies/mL upon resuming LA therapy and at week 256.

Safety

All participants in each group experienced ≥1 AE through week 256 (Table 3). Excluding ISRs, the most common AE was nasopharyngitis in the randomized Q8W/Q4W (45%) and extension-switch (25%) groups. Most participants in the randomized Q8W/Q4W (67%) and extension-switch (77%) groups reported AEs of maximum grade 1/2. The most common non-ISR, drug-related AEs in the randomized Q8W/Q4W groups were pyrexia (7%), back pain (3%), and fatigue (3%). No non-ISR, drug-related AE occurred in >1 participant in the extension-switch groups. Through week 256, 3 (3%) and 20 (17%) participants in the randomized Q8W and Q4W groups, respectively, had AEs leading to withdrawal, with 2 (2%)

Table 2. Virologic Outcomes at Week 256 by United States Food and Drug Administration Snapshot Algorithm

	ITT, Maintenance-Exposed, Randomized Population		Extension-Switch Population	
	Q8W IM	Q4W IM	Q8W IM	Q4W IM
Outcome	(n = 115)	(n = 115)	(n = 34)	(n = 10)
HIV-1 RNA <50 copies/mL	101 (88)	85 (74)	32 (94)	9 (90)
HIV-1 RNA ≥50 copies/mL	4 (3)	0	1 (3)	0
Discontinued for lack of efficacy	1 (<1)	0	1 (3)	0
Discontinued for other reasons	3 (3)[a]	0	…	…
No virologic data	10 (9)	30 (26)	1 (3)	1 (10)
Discontinued due to AE or death[b]	2 (2)[c]	18 (16)[d,e]	1 (3)[f]	1 (10)[g]
Discontinued for other reasons	8 (7)	11 (10)	…	…
Missing data during window but on study	0	1 (<1)	…	…

Data are presented as No. (%).

Abbreviations: AE, adverse event; HIV-1, human immunodeficiency virus type 1; IM, intramuscular; ITT, intention to treat; Q4W, every 4 weeks; Q8W, every 8 weeks.

[a]Includes consent withdrawal due to injection intolerability.

[b]Participants could have ≥1 AE leading to withdrawal.

[c]Chills, injection site pain, injection site pruritus, and pain (n = 1); hepatitis C virus infection (n = 1).

[d]Three deaths occurred due to epilepsy (unrelated to study treatment), toxicity to various agents (unrelated to study treatment), and myocardial infarction (drug related).

[e]Acute kidney injury, adjustment disorder with depressed mood, coronary artery disease, deep venous thrombosis, drug abuse, eosinophilic granulomatosis with polyangiitis, epilepsy, fatigue, hepatitis C virus infection, hypoesthesia, injection site nodule, injection site pain, lymphadenopathy, mesenteric vein thrombosis, metabolic acidosis, motor neuron disease, muscular weakness, myocardial infarction, portal vein thrombosis, prolonged QT interval, psychotic disorder, rash, respiratory tract infection, rhabdomyolysis, sinus tachycardia, splenic vein thrombosis, suicide attempt, and toxicity to various agents.

[f]Back pain, conjunctival hyperemia, erythema, and papular urticaria.

[g]Injection site pain.

Table 3. Summary of Adverse Events Through Week 256

	ITT, Maintenance-Exposed, Randomized Population		Extension-Switch Population	
	Q8W IM	Q4W IM	Q8W IM	Q4W IM
Preferred Term	(n = 115)	(n = 115)	(n = 34)	(n = 10)
Any AE	115 (100)	115 (100)	34 (100)	10 (100)
AE, excluding ISR[a]				
Nasopharyngitis	50 (43)	53 (46)	6 (18)	5 (50)
Diarrhea	35 (30)	30 (26)	3 (9)	2 (20)
Headache	29 (25)	26 (23)	3 (9)	0
Influenza	20 (17)	26 (23)	7 (21)	3 (30)
Back pain	20 (17)	26 (23)	5 (15)	3 (30)
Syphilis	32 (28)	22 (19)	2 (6)	2 (20)
Upper respiratory tract infection	28 (24)	26 (23)	5 (15)	1 (10)
Gastroenteritis	26 (23)	22 (19)	7 (21)	0
Grade ≥3 AE	39 (34)	38 (33)	7 (21)	3 (30)
Excluding ISR	31 (27)	35 (30)	4 (12)	2 (20)
Drug related, excluding ISR	4 (3)	7 (6)	0	0
SAE	25 (22)	27 (23)	6 (18)	1 (10)
Excluding ISR	25 (22)	27 (23)	6 (18)	1 (10)
Drug related	1 (<1)[b]	2 (2)[c]	0	0
Fatal SAE	0	3 (3)[d]	0	0
AE leading to withdrawal[e]	3 (3)	20 (17)	1 (3)	1 (10)
Excluding ISR	2 (2)[f]	18 (16)[g]	1 (3)[h]	0
Drug related	2 (2)	8 (7)	1 (3)	1 (10)[i]

Data are presented as No. (%).

Abbreviations: AE, adverse event; IM, intramuscular; ISR, injection site reaction; ITT, intention to treat; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event.

[a]AEs reported in >20% of participants in a treatment group.

[b]Delusion and depression.

[c]Chest pain and abdominal pain, dyspnea, flushing, and myocardial infarction (n = 1 participant each).

[d]Epilepsy (unrelated to study treatment), toxicity to various agents (unrelated to study treatment), and myocardial infarction (drug related) in 1 participant each.

[e]Participants could have >1 AE leading to withdrawal.

[f]Chills (drug related), hepatitis C virus infection, and pain (drug related).

[g]Acute kidney injury, coronary artery disease, deep venous thrombosis, drug abuse, eosinophilic granulomatosis with polyangiitis, epilepsy, fatigue, hepatitis C virus infection, hypoesthesia, lymphadenopathy, mesenteric vein thrombosis, metabolic acidosis, motor neuron disease, muscular weakness, portal vein thrombosis, respiratory tract infection, rhabdomyolysis, splenic vein thrombosis, squamous cell carcinoma of the lung, suicide attempt, and toxicity to various agents (all not drug related). Abdominal pain, adjustment disorder with depressed mood, chest pain, dyspnea, flushing, myocardial infarction, prolonged QT interval, psychotic disorder, rash, and sinus tachycardia (all drug related).

[h]Back pain, conjunctival hyperemia, erythema, and papular urticaria (all drug related).

[i]Injection site pain.

and 8 (7%) participants, respectively, reporting AEs leading to withdrawal that were treatment related. AEs leading to withdrawal reported in >1 participant in the randomized Q8W/Q4W groups were injection site pain (n = 2 in the Q8W group, n = 1 in the Q4W group) and hepatitis C virus infection (n = 1 in each group). Four non-drug-related thrombotic AEs leading to withdrawal were reported in 2 participants in the randomized Q4W group, 3 of which were abdominal and occurred in the same participant. Of 17 participants in the randomized Q4W group who withdrew because of AEs and had available follow-up viral load data, 16 maintained HIV-1 RNA <50 copies/mL at each follow-up assessment, 9 of whom switched to an oral ART regimen after discontinuing LA therapy. The remaining participant had an HIV-1 RNA measurement of 164 copies/mL 11 days after discontinuation and achieved HIV-1 RNA <50 copies/mL 1 month later; the posttreatment ART regimen of this participant was not available. One participant in each extension-switch group had drug-related AEs leading to withdrawal.

ISRs occurred in 38% of 21 179 total injections (mean injections per participant, 47 [range, 3–71]) administered in the randomized Q8W/Q4W groups and 26% of 2319 total injections (mean injections per participant, 27 [range, 5–45]) administered in the extension-switch groups (Table 4). Injection site pain was the most common ISR and most frequently reported overall AE in each group. Incidence of ISRs reduced over time in each group, remaining relatively stable from weeks 96 to 256 in the randomized Q8W and Q4W groups (Supplementary Figure 2). Most ISRs were grade 1/2. Median ISR duration was 2–3 days for each group. Five participants had ISRs leading to study withdrawal: 2 (2%) participants in the randomized Q8W group at weeks 8 and 24, 2 (2%) in the randomized Q4W group

Table 4. Event-Level Summary of Injection Site Reactions Through Week 256

Outcome	ITT, Maintenance-Exposed, Randomized Population		Extension-Switch Population	
	Q8W IM (n = 115)	Q4W IM (n = 115)	Q8W IM (n = 34)	Q4W IM (n = 10)
Injection, No.	7673	13 506	1503	816
ISR event, No.	3373	4702	429	182
Grade, No. (% of ISR events)				
1	2772 (82)	4151 (88)	358 (83)	143 (79)
2	571 (17)	527 (11)	64 (15)	36 (20)
3	24 (<1)	22 (<1)	7 (2)	3 (2)
4	0	0	0	0
Most common ISR event, No. (% of ISR events)				
Pain	2265 (67)	2936 (62)	368 (86)	166 (91)
Nodule	238 (7)	557 (12)	26 (6)	13 (7)
Pruritis	230 (7)	222 (5)	8 (2)	0
Swelling	200 (6)	248 (5)	9 (2)	2 (1)
Duration, d				
≤7	2964 (88)	3992 (85)	399 (93)	167 (92)
8–14	263 (8)	300 (6)	12 (3)	9 (5)
≥15	137 (4)	398 (8)	17 (4)	5 (3)
Median, d	3.0	3.0	3.0	2.0
Participants with ISR leading to withdrawal, No. (% of participants)[a]	2 (2)[b]	2 (2)[c]	0	1 (10)[d]

Abbreviations: IM, intramuscular; ISR, injection site reaction; ITT, intention to treat; Q4W, every 4 weeks; Q8W, every 8 weeks.

[a]Participants could have >1 ISR event leading to withdrawal.

[b]Injection site pain (n = 2), injection site induration (n = 1), injection site pruritis (n = 1), and injection site swelling (n = 1).

[c]Injection site nodule (n = 1) and injection site pain (n = 1).

[d]Injection site pain.

at weeks 208 and 224, and 1 (10%) in the extension-switch Q4W group at week 160. No fatal or serious ISRs were reported.

Serious AEs (SAEs) occurred in 52 (23%) and 7 (16%) participants in the randomized Q8W/Q4W and extension-switch groups, respectively (Table 3). The most frequently reported SAEs in the randomized Q8W/Q4W groups were acute kidney injury and suicide attempt; each SAE was not treatment related and occurred in 2 participants in the Q8W group and 1 participant in the Q4W group. All SAEs in the extension-switch groups occurred in 1 participant each, except for pneumonia (n = 2 in the Q8W group). No new AEs of clinical concern were reported during the extension period, except for 1 participant in the randomized Q4W group. This individual experienced SAEs of abdominal pain, chest pain, dyspnea, and flushing immediately after rilpivirine injection and before cabotegravir injection at week 256; all events resolved on the same day of onset and were considered by the investigator to be related to rilpivirine, so cabotegravir and rilpivirine were discontinued. Three participants died in the randomized Q4W group. One death occurred at week 30 in the maintenance period due to epilepsy, which was not related to study treatment. A second death occurred at week 223 (between week 220 and 224 study visits) of the extension period due to coronary atherosclerosis secondary to drug toxicity (possibly due to cocaine use) and was not related to study treatment. A third death due to myocardial infarction at week 139 of the extension period was considered by the investigator to be potentially study drug related.

Grade 3/4 treatment-emergent laboratory abnormalities of increased creatine kinase and lipase levels were reported in 13% and 8% of participants in the randomized Q8W/Q4W groups, respectively. Grade 3/4 laboratory abnormalities of increased total cholesterol and low-density lipoprotein cholesterol were each reported in 2 and 1 participants in the extension-switch Q8W and Q4W groups, respectively. Other grade 3/4 laboratory abnormalities were reported in ≤5% of participants in the randomized Q8W/Q4W and extension-switch groups. No clinically significant changes from baseline in electrocardiograms or vital signs were observed.

DISCUSSION

Long-acting therapy is a new option in HIV-1 therapeutics. This is the first report describing >2-year efficacy, safety, tolerability, and durability of cabotegravir + rilpivirine LA. Over approximately 5 years, cabotegravir + rilpivirine LA Q8W and Q4W demonstrated antiviral efficacy in virologically suppressed participants, with none meeting PDVF criteria after week 48. Cabotegravir + rilpivirine LA was well tolerated for both dosing regimens after approximately 5 years of treatment, consistent with the safety profile observed during the maintenance period

[9]. Adherence to injection visits was high through 5 years of treatment, with high treatment satisfaction reported with Q8W and Q4W dosing regimens at weeks 48 and 96 [9].

After approximately 5 years of treatment, 81% of participants randomized to LA therapy maintained virologic suppression. The lower rate of virologic suppression observed for the randomized Q4W (74%) vs Q8W (88%) group resulted from an increased proportion of participants with no virologic data at week 256 in the Q4W group, driven by discontinuations due to AEs or other nonvirologic reasons. Few discontinuations were related to ISRs. After switching to and receiving LA therapy for approximately 3 years, 93% of participants in the extension-switch groups maintained virologic suppression. No participants in any group met PDVF criteria after week 48. Through week 48, only 2 of 230 (<1%) participants who received LA therapy met PDVF criteria, both of whom were in the Q8W group [9]. The sustained virologic efficacy and rare occurrence of PDVFs over approximately 5 years in LATTE-2 demonstrate durability of cabotegravir + rilpivirine LA dosed Q4W and Q8W.

Additional support for the durability of cabotegravir + rilpivirine was provided by long-term results from LATTE [24]. After 5.5 years taking oral cabotegravir + rilpivirine, 8 (5%) participants met PDVF criteria, 5 of whom were initially taking the 10-mg cabotegravir dose. After completing LATTE, 90 participants entered the Oral (PO) to Long Acting (LA) Rollover (POLAR) study and received cabotegravir + rilpivirine LA every 2 months; no participants had HIV-1 RNA ≥50 copies/mL or met PDVF criteria after 1 year [25]. Three (1%) participants who received cabotegravir + rilpivirine LA through 96 weeks in FLAIR had confirmed virologic failure; none occurred after week 48 [11, 13]. Therefore, daily oral and monthly and every-2-months LA regimens of cabotegravir + rilpivirine demonstrate efficacy and durability as maintenance therapy for HIV-1 infection.

The overall safety profile at week 256 was generally consistent with data observed from LATTE-2 at week 96 and from the ATLAS, FLAIR, and ATLAS-2M phase 3 studies [9, 11, 12, 22]. Although ISRs were frequent, most were mild/moderate, of short duration, and decreased over time. Through approximately 5 years of LA therapy with 21 179 total injections, 4 (2%) participants from the randomized Q8W/Q4W groups withdrew due to ISRs, 2 of whom discontinued after ≤24 weeks. In approximately 3 years of LA therapy and 2319 total injections in the extension-switch groups, 1 (2%) participant withdrew due to an ISR after 60 weeks. The proportion of participants who withdrew due to AEs cumulatively through week 256 was higher in the randomized Q4W (17%) vs Q8W group (3%), a trend observed cumulatively through weeks 48 (6% vs <1%) and 96 (7% vs 2%) [9]. This trend did not occur in ATLAS-2M, with 2% of participants each in Q8W and Q4W groups withdrawing due to AEs through week 48 [22]. No specific trend of AEs leading to study withdrawal was observed in the randomized Q4W group, with most AEs leading to withdrawal considered unrelated to study treatment and each AE reported in 1 participant. Therefore, the increased rate of withdrawals due to AEs in the randomized Q4W group does not appear to be attributed to the dosing regimen. Overall, these results support the long-term safety of cabotegravir + rilpivirine LA with Q8W and Q4W dosing regimens.

Adherence to injection visits was high in LATTE-2, with 96% of injections occurring within the ±7-day dosing window. Most interruptions in scheduled injection dosing were planned, and temporary oral therapy with cabotegravir + rilpivirine was used to cover the period between injections. Each participant using oral dosing for planned treatment interruptions maintained virologic suppression when LA injections were resumed and through week 256, demonstrating the flexibility of this strategy. Strict patient adherence to scheduled injection visits may occasionally not be feasible in real-world situations (eg, holidays, prolonged travel, unforeseen life event, clinic closure); therefore, availability of oral dosing between injection visits provides a practical solution for managing planned LA treatment interruptions and maintaining treatment effectiveness.

This study had limitations. Sample sizes were small, particularly for the extension-switch groups. Participants were predominately male, and baseline $CD4^+$ cell count was restricted to ≥200 cells/μL, potentially limiting generalizability. Results from the maintenance period of LATTE-2 informed the selection of optimized LA dosing regimens for the phase 3 clinical program; thus, the cabotegravir + rilpivirine LA loading doses administered to randomized Q8W/Q4W groups differed from optimized loading doses used for the extension-switch groups, in phase 3 clinical studies, and the approved regimen [11, 12, 14, 16, 18, 19, 22].

Long-term data from LATTE-2 show high rates of efficacy and acceptable safety for cabotegravir + rilpivirine LA in virologically suppressed adults with HIV-1 infection. These results demonstrate durability and tolerability of intramuscular cabotegravir + rilpivirine LA injections administered monthly or every 2 months as maintenance therapy and an alternative to daily oral ART.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Supplementary Figure 1. Adherence to injection visits in participants from randomized Q8W and Q4W IM groups through week 256. Injection timelines were calculated by actual injection visit date minus the projected dosing visit date from day 1. Abbreviations: IM, intramuscular; Q4W, every 4 weeks; Q8W, every 8 weeks.

Supplementary Figure 2. Proportion of participants reporting ISRs over time in (*A*) randomized Q8W/Q4W groups through week 256 and (*B*) extension-switch groups from weeks 100 to 256. Data represent incidence of onset of ISR-related adverse events relative to the most recent IM injection

visit. Abbreviations: IM, intramuscular; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks. [a]Numbers of participants receiving IM injection in randomized Q8W and Q4W groups are listed for Q8W visits starting at day 1. [b]Numbers of participants receiving IM injection are listed at week 100 and for Q8W visits starting at week 104.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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