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Long-term effects of evolocumab in participants with HIV and dyslipidemia: Results from the open-label extension period

Short title (running head): evolocumab in HIV-patients with dyslipidemia

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Abstract:

Objectives: People with HIV (PWH) are at increased risk of atherosclerotic cardiovascular disease. Suboptimal responses to statin therapy in PWH may result from antiretroviral therapies (ART). This open-label extension study aimed to evaluate the long-term safety and efficacy of evolocumab up to 52 weeks in PWH.

Design: This final analysis of a multinational, placebo-controlled, double-blind (DB), randomized phase 3 trial evaluated the effect of monthly subcutaneous evolocumab 420 mg on low-density lipoprotein cholesterol (LDL-C) during the open-label period (OLP) following 24 weeks of DB period in PWH with hypercholesterolemia/mixed dyslipidemia.

All participants enrolled had elevated LDL-C or non-high-density lipoprotein cholesterol (non-HDL-C) and were on stable maximally tolerated statin and stable ART.

Methods: Efficacy was assessed by percent change from baseline in LDL-C, triglycerides (TGs) and atherogenic lipoproteins. Treatment-emergent adverse events (TEAEs) were examined.

Results: Of the 467 participants randomized in the DB period, 451 (96.6%) received at least 1 dose of evolocumab during the OLP (mean age of 56.4 years, 82.5% male, mean duration with HIV of 17.4 years). By the end of the 52-week OLP, the overall mean (SD) percent change in LDL-C from baseline was -57.8% (22.8 %). Evolocumab also reduced TGs, atherogenic lipid parameters (non-HDL-C, apolipoprotein B, total cholesterol, very-low-density lipoprotein cholesterol, and lipoprotein[a]), and increased HDL-C. TEAEs were similar between placebo and evolocumab during the OLP.

Conclusion: Long-term administration of evolocumab lowered LDL-C and non-HDL-C, allowing more PWH to achieve recommended lipid goals with no serious adverse events.

Trail Registration: NCT02833844

Video abstract: http://links.lww.com/QAD/C441

Keywords: PCSK9, HIV, ART, open label extension, safety, lipid levels

Introduction

With the advances in effective antiretroviral therapy (ART), most deaths in people with human immunodeficiency virus (PWH) are due to comorbidities, including cardiovascular disease (CVD).[1] The risk for atherosclerotic cardiovascular disease (ASCVD) is higher in PWH.[2,3] Traditional CVD risk factors, including dyslipidemia and active smoking, are overrepresented in the HIV population.[4,5] HIV-related factors, such as chronic inflammation, immune dysregulation, and ART-associated metabolic abnormalities, could also lead to atherothrombosis.[3,5,6] Thus, the U.S. cholesterol and the European dyslipidemia guidelines have classified HIV as a risk-enhancing factor for ASCVD.[7,8] Studies have shown that treating dyslipidemia with statin monotherapy is more complex and challenging in PWH due to toxic drug-drug interactions (DDIs).[9-11] Therefore, CVD prevention in this high-risk population remains an unmet need.

Evolocumab is a fully human monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and lowers low-density lipoprotein cholesterol (LDL-C) levels among participants with primary hypercholesterolemia and mixed dyslipidemia.[12] BEIJERINCK (NCT02833844), a randomized, double-blind, placebo-controlled, multinational trial, has demonstrated the lipid-lowering efficacy and safety of 24 weeks of evolocumab in PWH with hypercholesterolemia or mixed dyslipidemia.[13] The present study reports the final analysis of BEIJERINCK, which evaluated the long-term efficacy and safety of evolocumab in PWH during the open-label extension period (week 24 to 52).

Methods

Study Design and Participant Population

The design and primary results of the BEIJERINCK study have been previously published.[13,14] This trial had two phases: in the 24 weeks of double-blind (DB) treatment period, participants were randomized (2:1) to monthly subcutaneous evolocumab 420 mg or placebo, after which participants who received a dose of evolocumab at week 20 continued in an open-label period (OLP). During the OLP, all participants were treated with evolocumab 420 mg monthly through the end-of-study at week 52 (Fig 1). Eligible participants were adults with known HIV infection and receiving stable HIV therapy for ≥6 months prior to randomization. Participants were required to be on a maximally tolerated statin for ≥4 weeks before screening, which for some participants, could mean no statin at all due to statin intolerance or contraindication. Statin intolerance was defined as a trial of at least 2 statins with failure of at least one statin (due to rhabdomyolysis) or two statins (due to intolerable myopathy or myositis) and symptoms resolved or improved when statin dose was decreased or discontinued. Participants were to demonstrate fasting triglycerides ≤600 mg/dL and HIV viral load ≤50 copies/mL at screening, and cluster of differentiation 4 (CD4) ≥250 cells/mm3 and HIV viral load ≤200 copies/mL for ≥6 months prior to randomization. Detailed inclusion and exclusion criteria have been published previously. [14]

The study was conducted in accordance with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines. The protocol and the informed consent form were reviewed and approved by an institutional review board or independent ethics committee at each study center. All enrolled participants provided informed consent. Qualified researchers may request data from Amgen clinical studies: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/

Study Objectives

The primary safety objective was to characterize the safety and tolerability of long-term administration of evolocumab in PWH. Secondary objectives included the efficacy of long-term treatment with evolocumab on LDL-C, triglycerides (TGs) and atherogenic lipoproteins. Exploratory objectives included the evaluation of long-term treatment with evolocumab on biomarkers of inflammation, immune regulation, and thrombosis.

Statistical Analysis

This report's analyses included all participants who received at least 1 dose of open-label evolocumab during the OLP. Repeated-measures linear mixed-effects models assessed the efficacy endpoints. Multiplicity adjustment was performed to preserve the family-wise error rate at 0.05. Safety and exploratory endpoints were summarized descriptively.

Results

Study Population

The trial was conducted at 72 sites globally from May 22, 2017, to January 27, 2020. A total of 467 participants were enrolled and randomized 2:1 to the evolocumab 420 mg once monthly (n=310) or to the placebo (n=157) during the DB period. Of the 467 participants, 455 (97.4%) continued into the OLP and 451 (96.6%) received at least 1 dose of evolocumab during the OLP (Fig 2). Four (0.9%) participants discontinued the OLP early including one withdrawal of consent, one lost to follow-up, and two deaths (sarcomatoid carcinoma and constrictive pericarditis). During the OLP, participant disposition was similar between participants who received evolocumab and placebo during the DB period. The mean (standard deviation [SD]) exposure of evolocumab in the OLP was 27.5 (2.5) weeks.

Baseline characteristics

At baseline (week 0 before DB treatment), demographic characteristics are summarized in Table 1. The majority of the participants were middle-aged white males with a long duration of HIV infection (mean, 17.4 years) and a viral load of ≤50 copies/ml. A history of coronary artery disease was present in 28.6% of participants and cardiovascular risk factors were prevalent. Among the participants without ASCVD, 33.5% had intermediate or high 10-year ASCVD risk scores based on the ASCVD pooled cohort risk equations. Mean (SD) baseline

calculated LDL-C concentration was 133.5 (40.4) mg/dL. Other baseline lipid parameters are shown in Table 1. All participants received ART and 358 participants (79.4%) received statins at baseline. The 20.6% of participants who did not receive statins were statin intolerant or had a contraindication to statin use.

Safety Evaluation

During the OLP, 203 (45.0%) participants had a treatment-emergent adverse event (TEAE) (Table 2). Serious TEAEs occurred in 22 (4.9%) participants, but none was judged by the investigator as related to evolocumab or the device. The most frequently reported TEAEs were nasopharyngitis (3.3%), diarrhea (2.0%), sinusitis (2.0%), and bronchitis (2.0%).

The HIV viral load of ≤50 copies/mL remained in >96% of all participants during the OLP and mean CD4 counts did not change significantly. There were no trends that indicated clinically significant treatment-related laboratory abnormalities. No binding or neutralizing anti-evolocumab antibodies were detected during the OLP.

Efficacy Evaluation

As previously reported,[13] the mean percent change in LDL-C with evolocumab was -56.9% (95% CI: -61.6% to -52.3%) after 24 weeks of DB period. By the end of the OLP at week 52, mean (SD) percent change in LDL-C from baseline was -57.8% (22.8%) in all participants analyzed (Fig 3). Mean (SD) percent changes from baseline to week 52 in other lipids were as follows: high density lipoprotein cholesterol (HDL-C), 11.1% (19.5%); very-low-density lipoprotein cholesterol (VLDL-C), -13.0% (34.6%); non-HDL-C, -50.0% (21.0%); total cholesterol, -36.5% (16.9%); apolipoprotein B (ApoB), -47.1% (19.4%); TGs, -12.2% (37.7%); lipoprotein(a) (Lp[a]), -13.4% (37.4%); apolipoprotein A1 (ApoA1), 8.7% (12.6%), and remnant cholesterol, -19.6% (35.0%).

The long-term effects of evolocumab on the inflammatory biomarkers D-dimer, high sensitivity C reactive protein (hsCRP), CD 14, CD23, IL-6, IL-10, fibrinogen, CD163 and MCP-1 were analyzed (Supplemental Table 1, http://links.lww.com/QAD/C440). No significant differences between the treatment groups occurred during the DB period, and biomarkers levels did not change significantly from baseline to the end of the OLP.

Discussion

This final analysis of the BEIJERINCK open-label extension study represents the first report of long-term evolocumab treatment in PWH with hyperlipidemia and/or mixed dyslipidemia on maximally tolerated statin therapy. The study provides evidence that evolocumab was well tolerated and safe in PWH and achieved a persistent reduction in LDL-C of 58% through 52 weeks of exposure. Long-term treatment with evolocumab also led to sustained improvement in other lipid parameters including non-HDL-C, ApoB, total cholesterol, Lp(a), TGs, HDL-C, and VLDL-C. Overall, safety results were comparable to those seen in the DB period, and no new safety findings were observed.

Recently, the effects of evolocumab on endothelial function in PWH have been addressed.[15] In a single-center study including 19 PWH and 11 subjects with dyslipidemia, evolocumab improved coronary endothelial function in both groups using cine magnetic resonance imaging. Consistent with our present study, no significant effects of evolocumab on inflammatory biomarkers including hs CRP, IL-6, and soluble CD163 were found over 6 weeks. Therefore, whether evolocumab has pleiotropic effects beyond reducing LDL-C and/or a local anti-inflammatory effect on vascular function is not yet known. We did not find significant differences in the long-term effects of systemic inflammatory immune activation biomarkers between the treatment groups during the DB period or from baseline to the end of the OLP. We cannot exclude that there may be a local anti-inflammatory effect on the arterial wall.[16]

In PWH, the risk of DDI is significant, particularly between some statins (lovastatin, simvastatin and to a lower extent atorvastatin) and some antivirals (protease inhibitors, cobicistat) that could lead to serious and fatal rhabdomyolysis. Furthermore, the long-term risk of recurrent acute coronary events seems higher in PWH than in the general population.[17] The risk of DDI and the consequent lower usage rate of high-intensity statins may make it difficult to achieve LDL-C goals. Failure to appropriately lower LDL-C exposure, combined with the higher risk of primary and recurrent ischemic events in this population, creates substantial cardiovascular risk for PWH.[2,18] Therefore, intensive lipid management in PWH is essential for primary and secondary ASCVD prevention using a maximally tolerated statin, ezetimibe and PCSK9 inhibitor when appropriate per current dyslipidemia guidelines.[6,7]

PCSK9 inhibitors have demonstrated sustained efficacy in lowering LDL-C levels in patients with hypercholesterolemia. [19,20] The Open-Label Study of Long-term Evaluation Against LDL-C (OSLER-1) showed that evolocumab added to standard of care achieved a median LDL-C reduction of 56.5% in patients who have received treatment for up to 5 years.[20] Consistent with the data in patients without HIV, the BEIJERINCK OLE study indicated comparable long-term LDL-C reduction levels up to a year in PWH.

In the context of actual clinical practice, recent studies reported that therapeutic adherence and effectiveness of PCSK9 inhibitors were maintained in the long-term and adverse reactions (ARs) are sparse and mild.[21,22] Even though one of the most frequently reported ARs in trials was injection site reactions, the subcutaneous administration of PCSK9 inhibitors was well accepted by patients.[22] Additionally, multiple studies evaluating PCSK9 inhibitors treatment acceptance suggested a high level of drug acceptance and tolerability.[23-25] In the present OLE study, two (0.4%) participants had at least 1 device-related TEAE, including injection site hematoma in 1 (0.7%) participant and injection site reaction and application site pruritus in 1 (0.7%) participant. No device-related AE led to the discontinuation of the drug.

The BEIJERINCK study's strengths include a large, multinational enrollment of the PWH population at the moderate-to-high ASCVD risk levels and the stringent statin intolerance criteria. The potential bias of adverse event reporting is an inherent limitation to all open-

label studies. Another limitation of the study is that it is not designed to evaluate evolocumab's effect on CVD events in PWH.

Conclusions

In hypercholesterolemic PWH on maximally tolerated statin therapy, long-term treatment with evolocumab up to 52 weeks was safe and well-tolerated. No new safety findings were observed. The efficacy of evolocumab, including reducing LDL-C and improving other lipid parameters, was maintained throughout the OLP.

Contribution Statement:

All authors had full access to the data, participated in the interpretation of the results, contributed to writing the manuscript, and take responsibility for the integrity of the data and the accuracy of the analysis. Amgen Inc. provided funding for the study, was responsible for the design and conduct of the study and participated in the review of the manuscript in partnership with the independent authors. All authors approved the manuscript for submission.

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Study Investigators:

The following BEIJERINCK study investigators are listed by country center and in order of enrollment contribution: Australia: David Baker, Mark Bloch, Robert Finlayson, Jennifer Hoy, Kenneth Koh, Norman Roth; Belgium: Stephane De Wit, Eric Florence, Linos Vandekerckhove; Brazil: Bruno Caramelli, Jose Valdez Ramalho Madruga, Sandra Wagner Cardoso; Canada: Greg Bondy, Michael Gill, George Tsoukas, Sylvie Trottier, Marek Smieja; France: Franck Boccara, Christine Katlama, Fabrice Bonnet, Francois Raffi, Laurent Cotte, Jean-Michel Molina, Jacques Reynes; Greece: Antonios Papadopoulos, Simeon Metallidis, Vassilios Paparizos, Vasileios Papastamopoulos; Italy: Cristina Mussini, Massimo Galli, Andrea Antinori, Antonio Di Biagio, Pierluigi Viale; Poland: Andrzej Horban; Portugal: Nuno Marques, Daniel Coutinho, Joaquim Oliveira, Paula Freitas; Romania: Liliana-Lucia Preotescu, Iosif Marincu, Rodica Silaghi, Sorin Rugina; South Africa: Noluthando Mwelase, Sheena Kotze; Spain: Jose Ignacio Bernardino de la Serna, Vicente Estrada Perez, Esteban Martinez, Adrian Curran; Switzerland: Dominique Laurent Braun, Alexandra Calmy, Enos Bernasconi, Matthias Cavassini; United Kingdom: John Walsh, Julie Fox, Graeme Moyle; United States: Robert Rosenson, Jamie Morano, Jason Baker, Gerald Pierone, Carl Fichtenbaum, Paul Benson, Deborah Goldstein, Joseph Sacco, Princy Kumar, Robert Grossberg, Kara Chew, Christopher DeFilippi, Vilma Drelichman, Norman Markowitz, David Parenti, Katherine Doktor, Paul Thompson.

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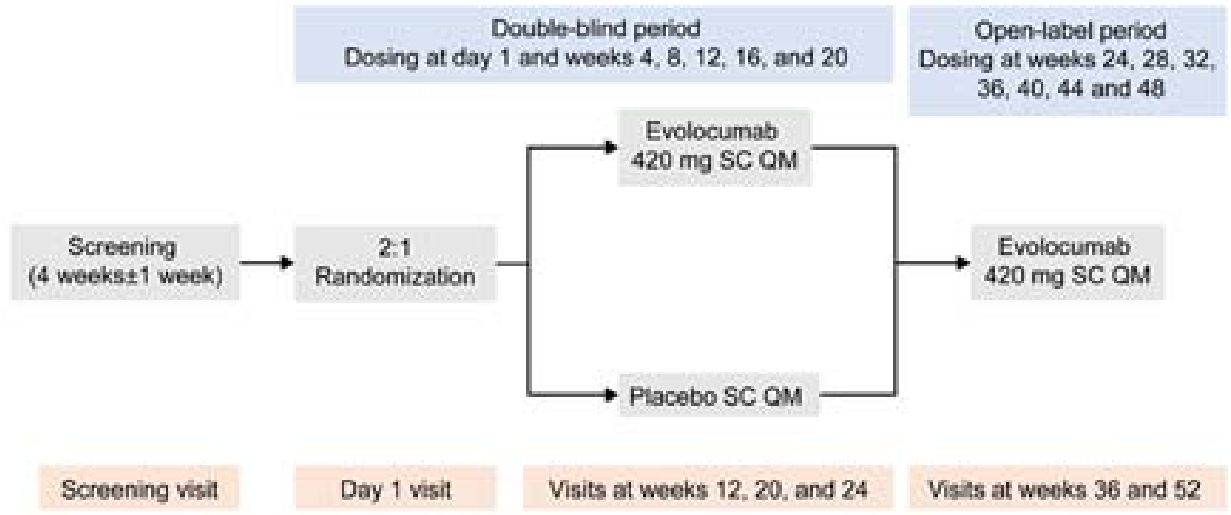
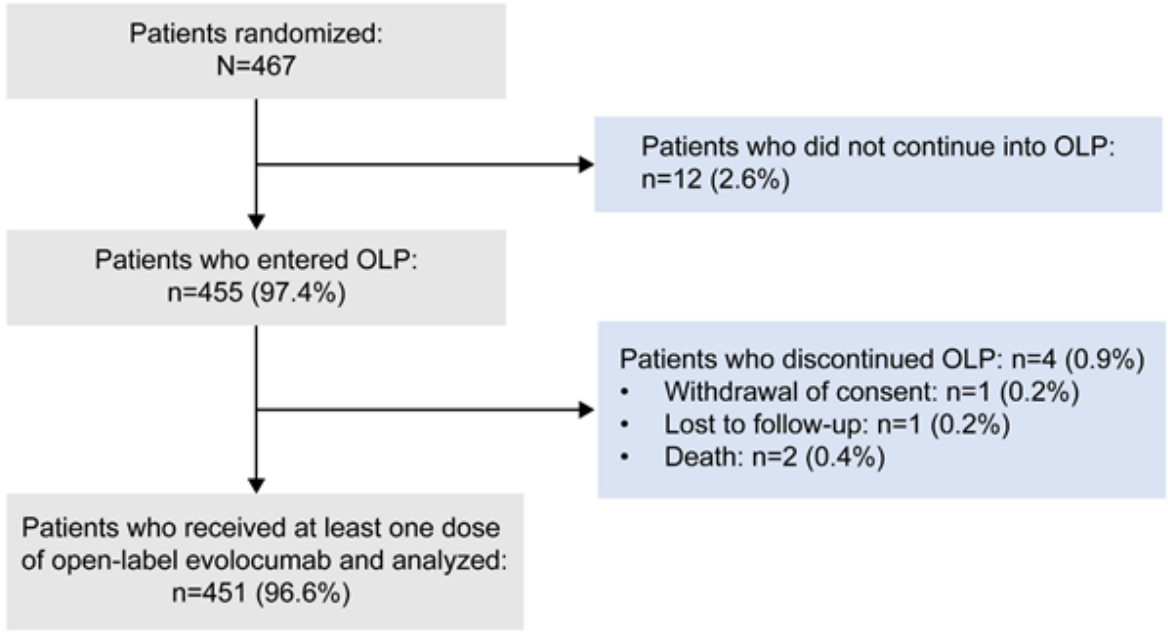
Figure 1. Study design.



QM: once monthly; SC: subcutaneous

Figure 2. Consort flow chart of participant disposition in the BEIJERINCK study.



OLP: open label period

Figure 3. Mean percent change in lipid parameters from baseline to end of study in BEIJERINCK.

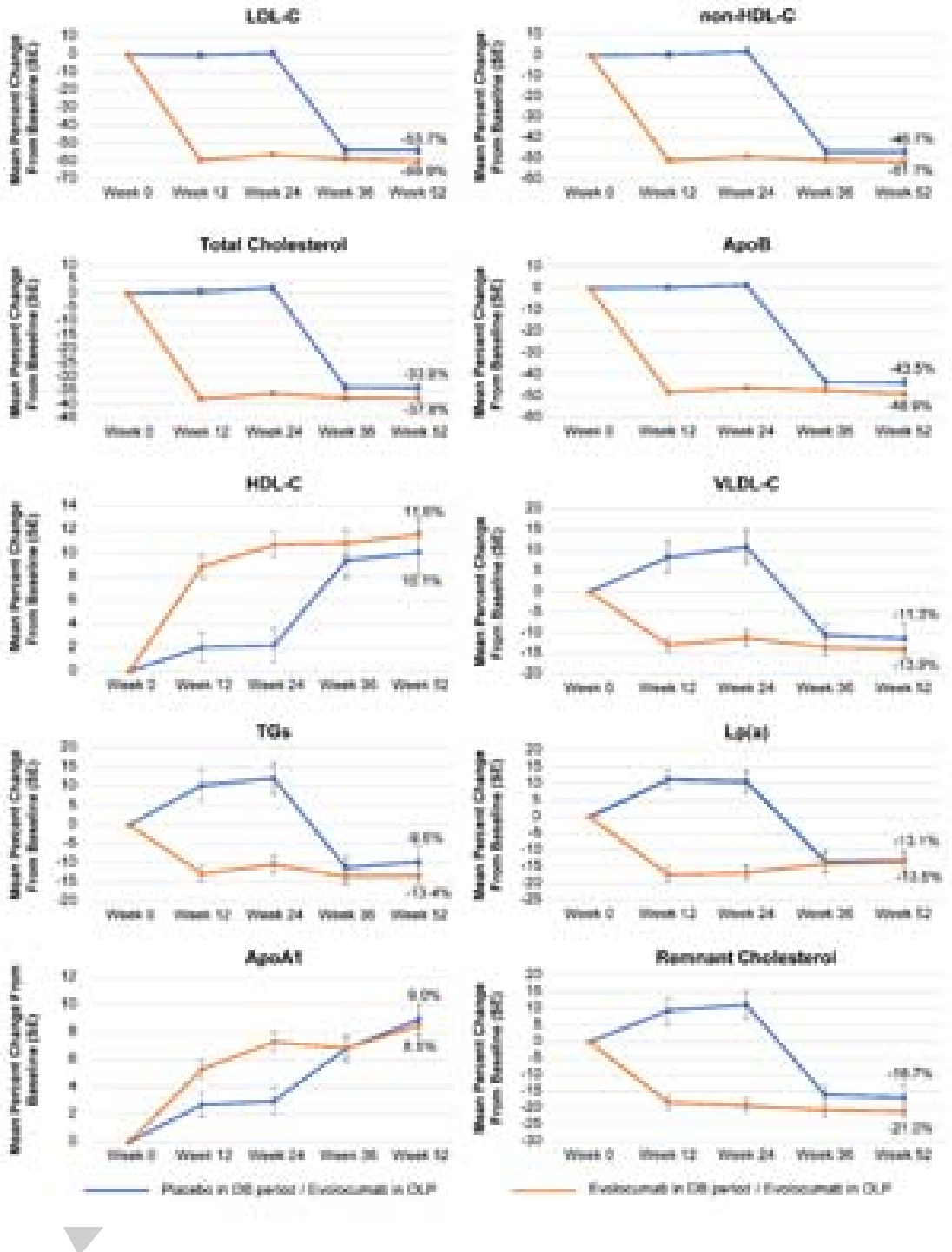


Table 1. Baseline demographics, clinical characteristics, medications and lipid levels.

	Patients who received placebo in DB period followed by evolocumab in OLP (N=152)	**Patients who received evolocumab in DB period followed by evolocumab in OLP (N=299)**	**All Patients (all received evolocumab) in OLP (N=451)**
Demographics			
Age (years)	56.1 ± 8.0	56.5 ± 9.1	56.4 ± 8.7
Male	116 (76.3)	256 (85.6)	372 (82.5)
Race			
White	121 (79.6)	240 (80.3)	361 (80.0)
Black or African American	25 (15.8)	50 (16.7)	74 (16.4)
Ethnicity			
Hispanic/Latino	21 (13.4)	41 (13.4)	62 (13.4)
Cardiovascular risk factors			
Hypertension	65 (42.8)	153 (51.2)	218 (48.3)
Low HDL-C [a]	45 (29.6)	99 (33.1)	144 (31.9)
Current cigarette smoking	43 (28.3)	80 (26.8)	123 (27.3)
Type 2 diabetes mellitus	24 (15.8)	50 (16.7)	74 (16.4)
BMI (kg/m^2)	26.7 ± 4.7	26.9 ± 4.7	26.9 ± 4.7
10-year ASCVD risk scores in the non-ASCVD cohort [b]			
High risk (>20%)	9 (5.9)	27 (9.0)	36 (8.0)
Intermediate risk (≥7.5% to ≤20%)	34 (22.4)	81 (27.1)	115 (25.5)
Borderline risk (≥5% to ≤7.5%)	0 (0.0)	0 (0.0)	0 (0.0)
Low risk (<5%)	57 (37.5)	80 (26.8)	137 (30.4)
Coronary artery disease	45 (29.6)	84 (28.1)	129 (28.6)
Cerebrovascular or peripheral arterial	13 (8.6)	45 (15.1)	58 (12.9)
Antiretroviral therapy			
NRTI	124 (81.6)	240 (80.3)	364 (80.7)
Integrase inhibitor	87 (57.2)	153 (51.2)	240 (53.2)
Protease inhibitor	58 (38.2)	127 (42.5)	185 (41.0)

Ritonavir-boosted regimen	44 (28.9)	98 (32.8)	142 (31.5)
Cobicistat-boosted regimen	37 (24.3)	57 (19.1)	94 (20.8)
NNRTI	55 (36.2)	120 (40.1)	175 (38.8)
Lipid-lowering therapy			
Statins	118 (77.6)	240 (80.3)	358 (79.4)
Ezetimibe	35 (23.0)	52 (17.4)	87 (19.3)
Fibrates	17 (11.2)	28 (9.4)	45 (10.0)
Lipid levels			
LDL-C (mg/dL) [c]	133.9 ± 40.4	133.4 ± 40.5	133.5 ± 40.4
Non-HDL-C (mg/dL)	169.3 ± 46.9	173.1 ± 46.1	171.8 ± 46.4
ApoB (mg/dL)	112.2 ± 27.1	113.9 ± 26.5	113.3 ± 26.7
HDL-C (mg/dL)	50.3 ± 14.9	47.3 ± 13.2	48.3 ± 13.9
Total Cholesterol (mg/dL)	219.6 ± 47.4	220.4 ± 45.9	220.1 ± 46.4
VLDL-C (mg/dL)	35.9 ± 24.5	41.2 ± 25.2	39.4 ± 24.1
TG (mg/dL)	175.2 ± 91.7	203.0 ± 116.3	193.6 ± 109.3
Lp(a) (nmol/L)	53.8 (20.0, 184.5)	54.5 (15.5, 185.5)	54.5 (18.0, 185.5)
Remnant Cholesterol (mg/dL) [d]	35.4 ± 20.3	39.8 ± 20.9	38.3 ± 20.8
PCSK9 serum level (ng/ml)	559.6 ± 202.7	536.9 ± 180.1	544.6 ± 188.1
hsCRP (mg/L)	1.7 (0.9, 3.6)	2.1 (1.1, 4.3)	1.9 (1.1, 4.1)

Values are mean ± SD, n (%), or median (Q1, Q3).

[a] Defined as HDL-C <40 mg/dL in men and <50 mg/dL in women. [b] 2018 ACC/AHA Pooled Cohort Risk Equations. These risk scores are only derived for the primary prevention patients (n=288). [c] Ultracentrifugation LDL-C was used when calculated LDL-C was <40 mg/dL or triglycerides were >400 mg/dL. [d] Remnant cholesterol was calculated as total cholesterol minus LDL-C and HDL-C from the same blood sample.[18]

ACC/AHA: American College of Cardiology/American Heart Association; ApoB: apolipoprotein B; ASCVD: atherosclerotic cardiovascular disease; DB: double-blind; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein(a); NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; OLP: open-label period; PCSK9: proprotein convertase subtilisin/kexin type 9; Q: quartile; TG: triglyceride; VLDL-C: very low–density lipoprotein cholesterol.

Table 2. Safety evaluation.

	Patients who received placebo in DB period followed by evolocumab in OLP (N=152)	**Patients who received evolocumab in DB period followed by evolocumab in OLP (N=299)**	**All Patients (all received evolocumab) in OLP (N=451)**
TEAEs	67 (44.1)	136 (45.5)	203 (45.0)
Grade [a] ≥2	44 (28.9)	90 (30.1)	134 (29.7)
Grade ≥3	7 (4.6)	22 (7.4)	29 (6.4)
Grade ≥4	2 (1.3)	3 (1.0)	5 (1.1)
Fatal TEAEs	0 (0.0)	1 (0.3)	1 (0.2)
Serious TEAEs	8 (5.3)	14 (4.7)	22 (4.9)
Leading to discontinuation of Open-Label IP	0 (0.0)	2 (0.7)	2 (0.4)
Most common TEAEs (≥2% among patients in any treatment group)			
Nasopharyngitis	6 (3.9)	9 (3.0)	15 (3.3)
Diarrhea	1 (0.7)	8 (2.7)	9 (2.0)
Sinusitis	1 (0.7)	8 (2.7)	9 (2.0)
Bronchitis	2 (1.3)	7 (2.3)	9 (2.0)

Values are n (%).

[a] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or later grading were used for severity assessments.

DB: double-blind; IP: investigational product; OL, open-label; TEAE: treatment-emergent adverse event.