Evolocumab Use In Patients With Human Immunodeficiency Virus and Dyslipidemia: Final Results of the Open Label Extension Period (BEIJERINCK)

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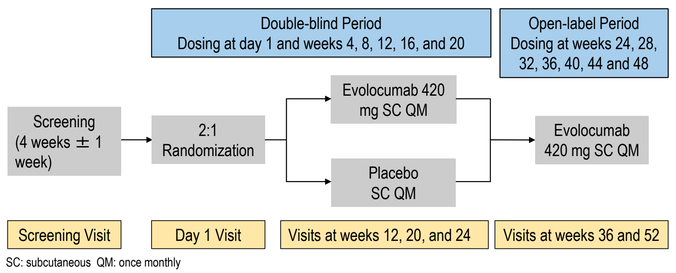
BACKGROUND

- People living with HIV (PLHIV) have increased risk for Atherosclerotic Cardiovascular Disease (ASCVD) events.[1] Treatment of dyslipidemic PLHIV remains challenging under current guidelines due to drug-drug interactions (DDIs) with certain classes of antiretroviral agents and statins.[2-4]
- Evolocumab, a fully human monoclonal antibody that binds to and prevents circulating PCSK9-mediated LDLR degradation on hepatocytes, is safe, well-tolerated, and has been demonstrated to reduce LDL-C and other lipid parameters in patients with dyslipidemia and/or hypercholesterolemia.[5]
- BEIJERINCK (NCT02833844), a randomized, double-blind, placebo-controlled, multinational trial, has demonstrated the lipid-lowering efficacy and safety of 24 weeks of evolocumab in PLHIV with hypercholesterolemia or mixed dyslipidemia who received maximally tolerated statin therapy.[6]
- The present study reports the final analysis of BEIJERINCK which evaluated the long-term efficacy and safety of evolocumab in PLHIV during the open-label extension period (week 24 to 52).

METHODS AND STUDY OBJECTIVES

- After 24 weeks of double-blind period (DBP), patients who received a dose of study drug at week 20 entered into the open-label period (OLP) during which all patients were treated with 420 mg evolocumab subcutaneously (SC) once monthly (OM). The OLP continued through the end-of-study at week 52. (**Figure 1**)
- All analyses were descriptive and based on the subjects who received at least 1 dose of evolocumab during OLP.
- The primary safety objective was to characterize the safety and tolerability of long-term administration of evolocumab.
- Secondary and exploratory objectives were to characterize the efficacy of long-term administration of evolocumab as assessed by percent changes from baseline in LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), very LDL-C (VLDL-C), and triglycerides (TGs).

Figure 1. Study Design



SC: subcutaneous QM: once monthly

MAIN PATIENT INCLUSION AND EXCLUSION CRITERIA

Main inclusion criteria[7]

- ≥ 18 years of age (male/female)
- HIV infection and received ART for ≥ 6 months pre-randomization
- HIV viral load of ≤ 50 copies/ml
- On maximally-tolerated statin therapy for ≥ 4 weeks pre-screening
- Patients with ASCVD: LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL (fasting)
- Patients without ASCVD: LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 130 mg/dL (fasting)

Main exclusion criteria[7]

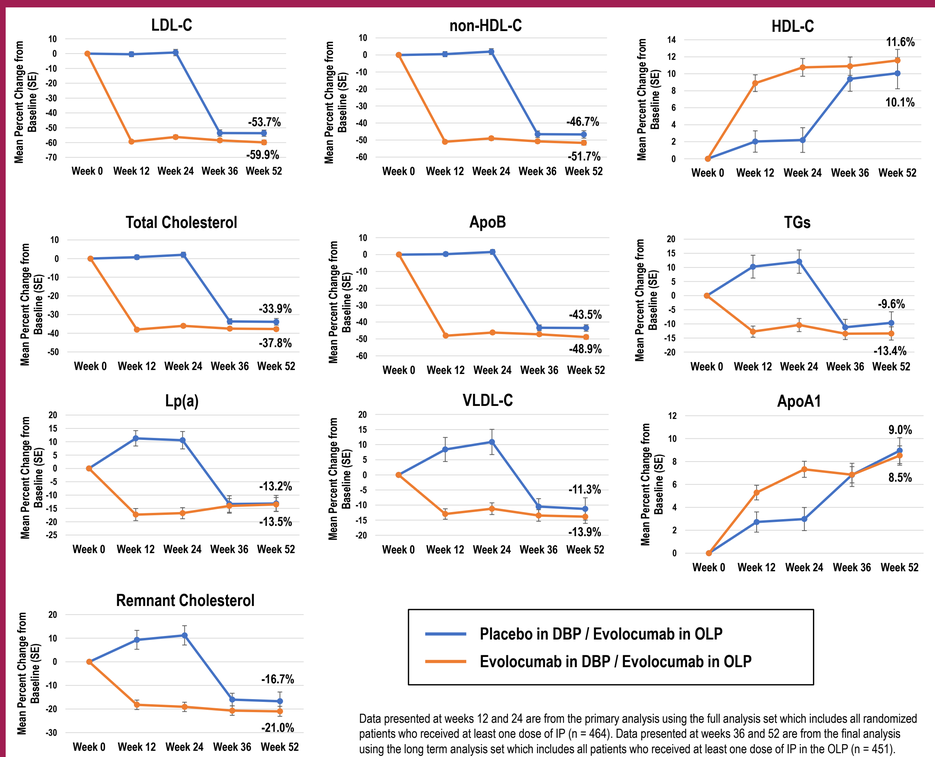
- Received lipid-lowering and ART therapy known to have significant DDIs
- Received CETP inhibitor (12 months pre-randomization), evolocumab, or any other PCSK9 inhibitor (any time)
- Known opportunistic infection/AIDS-defining illness within one year before randomization
- Known illness:
  - MI, unstable angina, percutaneous coronary intervention, coronary artery bypass graft/stroke within three months before randomization
  - Type 1, new-onset (HbA1c ≥ 6.5%) or poorly controlled (HbA1c ≥ 10%) type 2 diabetes during screening
  - Uncontrolled hypertension (systolic BP > 180 mmHg; diastolic BP > 100 mmHg) during screening
  - Malignancy within five years before randomization
  - Persistent active liver disease or severe hepatic dysfunction; estimated glomerular filtration rate < 30 mL/min/1.73 m^2 during screening)
- Fasting triglycerides > 600 mg/dL; CD4 count < 250 cells/mm^3; HIV viral load > 200 ml (or > 50 copies/ml at screening) within six months before randomization

Table 4. Patient Incident of Treatment Emergent Adverse Events (TEAEs) in OLP

	Placebo in DBP / EvoMab in OLP (N = 152)	EvoMab in DBP / EvoMab in OLP (N = 299)	All Subjects / EvoMab in OLP (N = 451)
Treatment Emergent Adverse Events (TEAEs)	**67 (44.1)**	**136 (45.5)**	**203 (45.0)**
Grade* ≥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)
Most common TEAEs (≥ 2% among all subjects)			
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)

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

Figure 3. Long-term Efficacy of Evolocumab



Data presented at weeks 12 and 24 are from the primary analysis using the full analysis set which includes all randomized patients who received at least one dose of IP (n = 464). Data presented at weeks 36 and 52 are from the final analysis using the long term analysis set which includes all patients who received at least one dose of IP in the OLP (n = 451).

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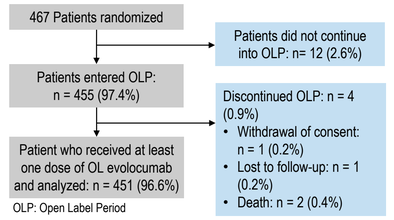
RESULTS

- During the OLP, overall median (Q1, Q3) exposure of evolocumab was 24.1 (24.1, 24.2) weeks.
- Patient disposition in the OLP is shown in **Figure 2.**
- The patients in OLP are representative of the HIV population with baseline characteristics. (**Table 1, 2 & 3**)
- During the OLP, 203 (45.0%) patients had a treatment-emergent adverse event (TEAE). The patient incidence of serious TEAEs and TEAEs leading to investigational product (IP) discontinuation were similar between DBP and OLP. (**Table 4**)
- Evolocumab reduced LDL-C from baseline by ~56% in the 24-week DBP and open-label evolocumab maintained the LDL-C reduction (~58%) at week 52. (**Figure 3**)

Figure 2. Patient Disposition



OLP: Open Label Period

Table 1. Baseline Demographics and Clinical Characteristics

Baseline Characteristics	Placebo in DBP / EvoMab in OLP (N = 152)	EvoMab in DBP / EvoMab in OLP (N = 299)	All Subjects / EvoMab in OLP (N = 451)
Demographics			
Age in years, mean (SD)	56.1 (8.0)	56.5 (9.1)	56.4 (8.7)
Sex, male, n (%)	116 (76.3)	256 (85.6)	372 (82.5)
White race, n (%)	121 (79.6)	240 (80.3)	361 (80.0)
Black or African American race, n (%)	25 (15.8)	50 (16.7)	74 (16.4)
Hispanic/Latino ethnicity, n (%)	21 (13.4)	41 (13.4)	62 (13.4)
Cardiovascular risk factors, n (%)			
Hypertension	65 (42.8)	153 (51.2)	218 (48.3)
Low HDL-C	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), mean (SD)	26.7 (4.7)	26.9 (4.7)	26.9 (4.7)
Coronary artery disease	45 (29.6)	84 (28.1)	129 (28.6)

Table 2. Baseline Medication Use

Baseline Characteristics	Placebo in DBP / EvoMab in OLP (N = 152)	EvoMab in DBP / EvoMab in OLP (N = 299)	All Subjects / EvoMab in OLP (N = 451)
Antiretroviral therapy, n (%)			
NRTI	124 (81.6)	240 (80.3)	364 (80.7)
Boosted NNRTI	55 (36.2)	120 (40.1)	175 (38.8)
Integrase inhibitor	87 (57.2)	153 (51.2)	240 (53.2)
Boosted protease inhibitor	58 (38.2)	127 (42.5)	185 (41.0)
Lipid-lowering therapy			
Statins, n (%)	118 (77.6)	240 (80.3)	358 (79.4)
Ezetimibe, n (%)	35 (23.0)	52 (17.4)	87 (19.3)
Fibrates, n (%)	17 (11.2)	28 (9.4)	45 (10.0)

Table 3. Baseline Lipid Levels

Baseline Characteristics	Placebo in DBP / EvoMab in OLP (N = 152)	EvoMab in DBP / EvoMab in OLP (N = 299)	All Subjects / EvoMab in OLP (N = 451)
Lipid levels			
LDL-C (mg/dL), Mean (SD)	133.9 (40.4)	133.4 (40.5)	133.5 (40.4)
Non-HDL-C (mg/dL), Mean (SD)	169.3 (46.9)	173.1 (46.1)	171.8 (46.4)
ApoB (mg/dL), Mean (SD)	112.2 (27.1)	113.9 (26.5)	113.3 (26.7)
HDL-C (mg/dL), Mean (SD)	50.3 (14.9)	47.3 (13.2)	48.3 (13.9)
Total Cholesterol (mg/dL), Mean (SD)	219.6 (47.4)	220.4 (45.9)	220.1 (46.4)
VLDL-C (mg/dL), Mean (SD)	35.9 (24.5)	41.2 (25.2)	39.4 (24.1)
TG (mg/dL), Mean (SD)	175.2 (91.7)	203.0 (116.3)	193.6 (109.3)
Lp(a) (nmol/L), Median (Q1, Q3)	53.8 (20.0, 184.5)	54.5 (15.5, 185.5)	54.5 (18.0, 185.5)
PCSK9 (ng/ml), Mean (SD)	559.6 (202.7)	536.9 (180.1)	544.6 (188.1)
hsCRP (mg/L), Median (Q1, Q3)	1.7 (0.9, 3.6)	2.1 (1.1, 4.3)	1.9 (1.1, 4.1)

LDL-C, Low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; ApoB, apolipoprotein B; VLDL, very low–density lipoprotein cholesterol; TG, Triglyceride; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; hsCRP, high-sensitivity C-reactive protein

CONCLUSIONS

- **In PLHIV on maximally-tolerated statin therapy, long term treatment (up to 52 weeks) with evolocumab therapy demonstrated sustained, substantial reduction of LDL-C of 58%.**
- **Long-term treatment with evolocumab was well-tolerated and safe in PLHIV.**
- **Treatment with evolocumab also reduced triglycerides, atherogenic lipid parameters (non-HDL-C, ApoB, total Cholesterol, VLDL-C and Lp[a]), and increased HDL-C.**

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