FOURIER-OLE Trial

Prezentuje

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PCSK9-i (MAB, biologická léčba hypercholesterolémie)

- **Alirocumab**
- **Bococizumab**
- **Evolocumab**

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- **Alirocumab** **(ODYSSEY)**
- **Bococizumab** **(SPIRE)**
- **Evolocumab** **(PROFICIO)**

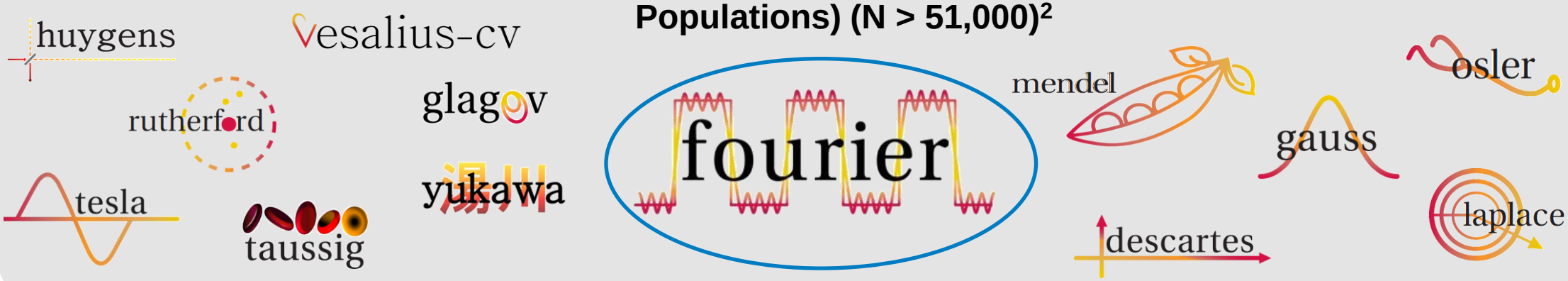
PCSK9-i (MAB, biologická léčba hypercholesterolémie)

- Alirocumab (ODYSSEY)
- Bococizumab (SPIRE)
- **Evolocumab (PROFICIO)**

The FOURIER OUTCOMES Trial Is Part of the Robust PROFICIO Clinical Development Program

Evolocumab, a PCSK9i, has consistently demonstrated significant lipid-lowering effects in phase 2 and 3 trials, with a favorable safety profile[1]

PROFICIO (Program to Reduce LDL-C and CV Outcomes Following Inhibition of PCSK9 in Different Populations) (N > 51,000)[2]



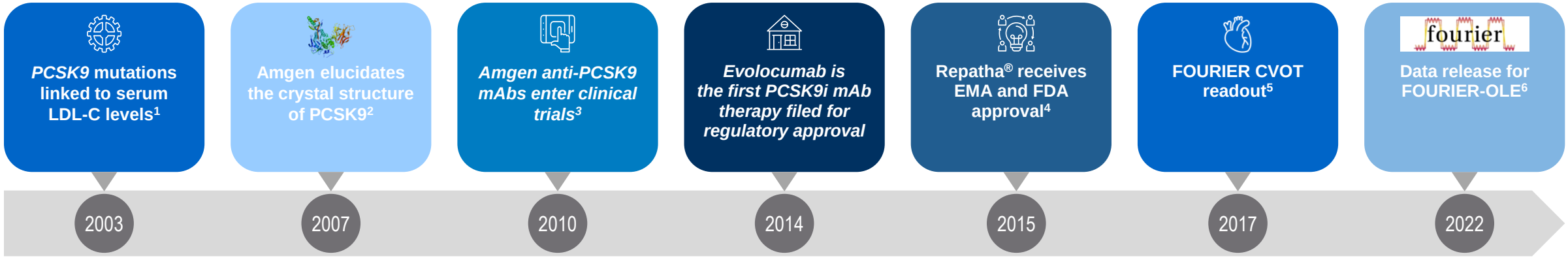
FOURIER was designed to evaluate the clinical efficacy and safety of evolocumab when added to high-intensity or moderate-intensity statin therapy in patients with clinically evident ASCVD[1,3]

AE = adverse event; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; LDL-C = low-density lipoprotein cholesterol; LTFU = long-term follow-up; PCSK9 = proprotein convertase subtilisin/kexin type 9; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor

1. Sabatine MS, et al. *Am Heart J*. 2016;173:94-101. 2. Data on File, Amgen; [1]; 2022. 3. Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722.

Background
Development of Repatha® (evolocumab)

7 Years From Initial Human Studies to Cardiovascular Outcomes Trial Read-out[1-6]



50 Number of clinical trials[7]

> 51,000 Number of patients in clinical trials[7]

> 1.7 million Cumulative postmarketing patient exposure[8,*]

*Cumulative postmarket exposure estimates from July 2015 through July 2022 in patients that have received at least one dose administration of the product. The number of patients receiving at least one administration is estimated using worldwide unit sales data and prescription claims data and applying utilization assumptions to calculate the unique number of patients. Sources include Amgen Finance Electronica Data Warehouse, IQVIA prescription claims, and MarketScan claims data. The estimates assume patient self-administration based on filled prescriptions[9]

CVOT = cardiovascular outcome trial; EMA = European Medicines Agency; FDA = Food and Drug Administration; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; LDL-C = low-density lipoprotein cholesterol; mAb = monoclonal antibody; OLE = open-label extension; PCSK9 = proprotein convertase subtilisin/kexin type 9; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor

1. Abifadel M, et al. *Nat Genet*. 2003;34:154-156. 2. Piper DE, et al. *Structure*. 2007;15:545-552. 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01133522. Accessed November 1, 2022. 4. Repatha® (evolocumab) prescribing information, Amgen. 5. Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722. 6. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119. 7. Data on file, Amgen; [1]; 2022. 8. Data on file, Amgen; [2]; 2022. 9. Data on file update, Amgen; October 2022.

FOURIER Parent Trial
Study Design

Randomized, double-blind, placebo-controlled, multinational clinical trial[1-3]

Screening/Key Eligibility Criteria

- Age 40–85 years
- MI, stroke, or PAD
- Additional risk factors (one major or two minor)*
- Optimal background lipid therapy (including effective dose of statin ± ezetimibe)
- LDL-C ≥ 70 mg/dL† or non–HDL-C ≥ 100 mg/dL

Randomization 1:1

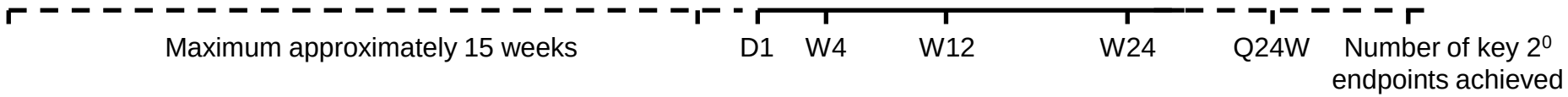
Evolocumab SC
140 mg Q2W or 420 mg QM
(per patient preference)
N = 13,784

Placebo SC
Q2W or QM
(per patient preference)
N = 13,780

End of Study

Endpoints

- **Primary:** Composite of CV death, MI, stroke, hospitalization for UA, or CoR
- **Key secondary:** Composite of CV death, MI, or stroke
- **Other secondary:** All-cause death, CoR; CV death or hospitalization for heart failure; ischemic stroke or TIA



*Major additional risk factors: diabetes, current smoker, MI, or nonhemorrhagic stroke at ≤ 6 months of screening. Minor additional risk factors: history of non-MI–related coronary revascularization, metabolic syndrome, LDL-C ≥ 130 mg/dL, or non–HDL-C ≥ 160 mg/dL

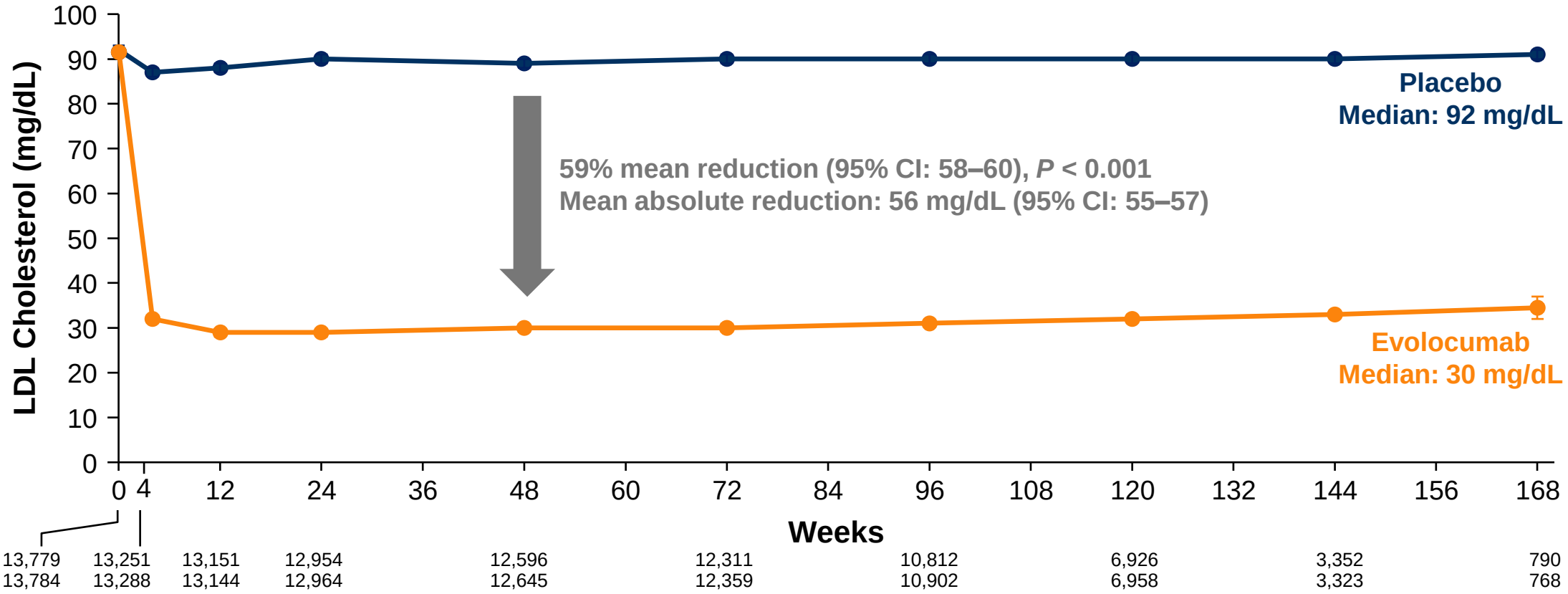
†Fasting LDL-C

CoR = coronary revascularization; CV = cardiovascular; D = day; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease; Q2W = once every 2 weeks; Q24W = once every 24 weeks; QM = once a month; SC = subcutaneous; TIA = transient ischemic attack; UA = unstable angina; W = week

1. Sabatine MS, et al. *Am Heart J*. 2016;173:94-101. 2. Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722. 3. Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722; supplementary material.

FOURIER Parent Trial

Key Results



No. at risk													
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6,926	3,352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6,958	3,323	768

LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs < 0.1% in the placebo group

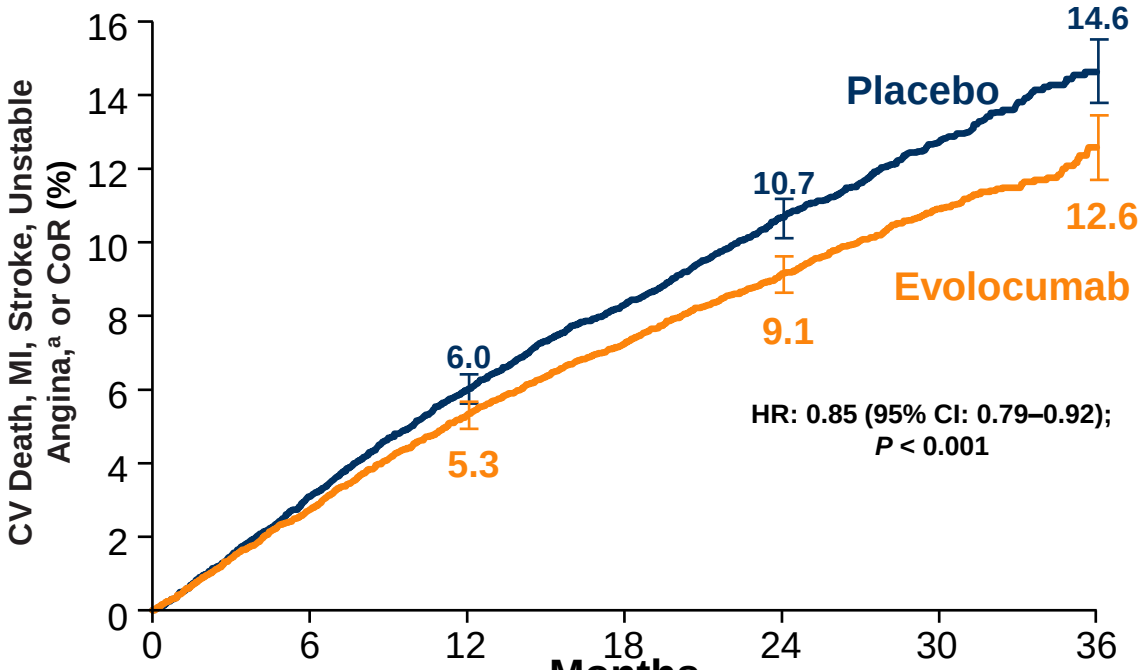
Data shown are median values with 95% CIs in the two arms

CI = confidence interval; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol

Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.

FOURIER Parent Trial

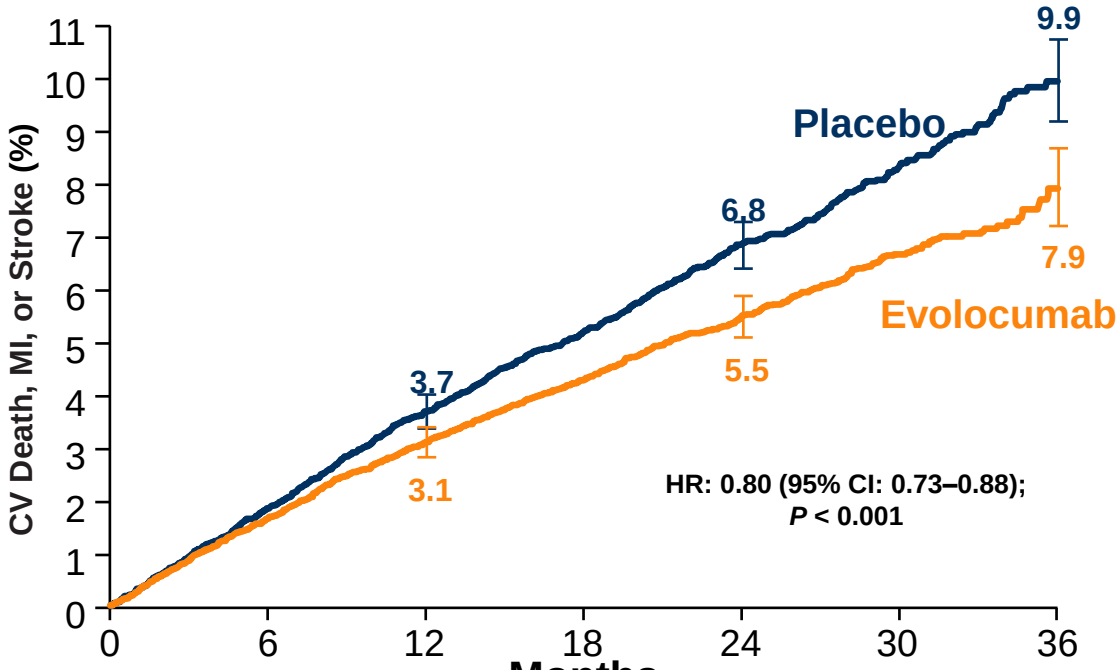
Key Results



No. at risk

Placebo	13,780	13,278	12,825	11,871	7,610	3,690	686
Evolocumab	13,784	13,351	12,939	12,070	7,771	3,746	689

Primary Endpoint



No. at risk

Placebo	13,780	13,449	13,142	12,288	7,944	3,893	731
Evolocumab	13,784	13,501	13,241	12,456	8,094	3,935	724

Key Secondary Endpoint

Patients receiving evolocumab experienced a 15% relative risk reduction in 5-point MACE* and 20% reduction in 3-point MACE† relative to those receiving placebo

[a]Hospitalization for unstable angina
*5-point MACE: CV death, MI, stroke, hospitalization for unstable angina, or CoR
†3-point MACE: CV death, MI, stroke
CI = confidence interval; CoR = coronary revascularization; CV = cardiovascular; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction

Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.

FOURIER-OLE Trial
Rationale

- Evolocumab, a fully human mAb, has shown to reduce LDL-C by approximately 60%[1]
- A prespecified exploratory analysis showed lower rates of MACEs, including CV death and death from coronary heart disease, in patients treated with evolocumab from the start compared with patients who initially received placebo in the parent FOURIER study
  - 20% RRR for CV death, MI, or stroke (HR = 0.80 [95% CI: 0.68–0.93]; *P* = 0.003)[2]
  - 23% RRR for CV death (HR = 0.77 [95% CI: 0.60–0.99]; *P* = 0.04)[2]
  - 35% for death from coronary heart disease (HR = 0.65 [95% CI: 0.48–0.90]; *P* = 0.008)[2]
- Notably, prolonged exposure to evolocumab exhibited greater benefit relative to placebo[1]

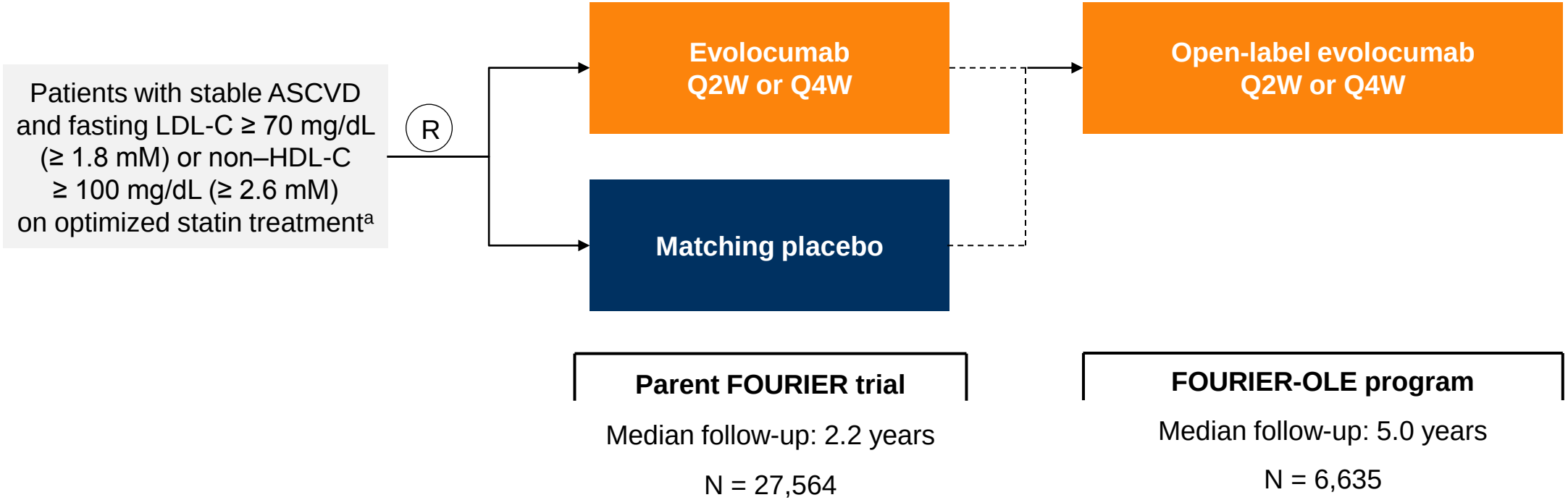
The FOURIER-OLE study was designed to capture longer-term data on the safety, tolerability, lipids levels, and risk of major adverse CV events* with continued evolocumab exposure following completion of the parent FOURIER trial[2]

*Limitations to the FOURIER-OLE include but are not limited to: all patients in the extension program were treated with open-label evolocumab resulting in no concurrent placebo arm during this period; CV outcomes were prespecified for the current analysis, but considered exploratory; *P* values are nominal and not adjusted for multiplicity[2]

CI = confidence interval; CV = cardiovascular; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; mAb = monoclonal antibody; MACE = major adverse cardiovascular event; MI = myocardial infarction; OLE = open-label extension; RRR = relative risk reduction

1. Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722. 2. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

FOURIER-OLE Trial
Study Design

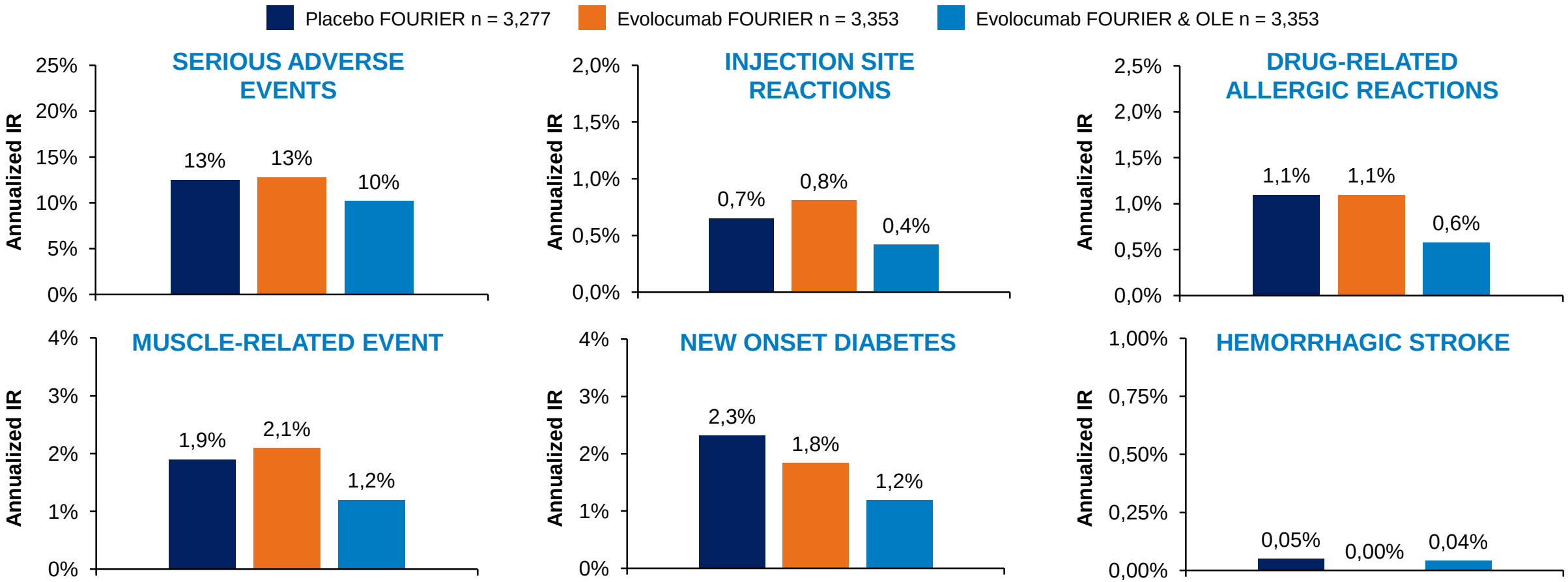


[a]Patients must be on a high-intensity statin but must have been on at least atorvastatin at a dose of 20 mg daily or its equivalent

ASCVD = atherosclerotic cardiovascular disease; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; OLE = open-label extension; Q2W = once every 2 weeks; Q4W = once every 4 weeks

1. Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722. 2. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

FOURIER-OLE Trial
Key Results: Annual Incidence of AEs*

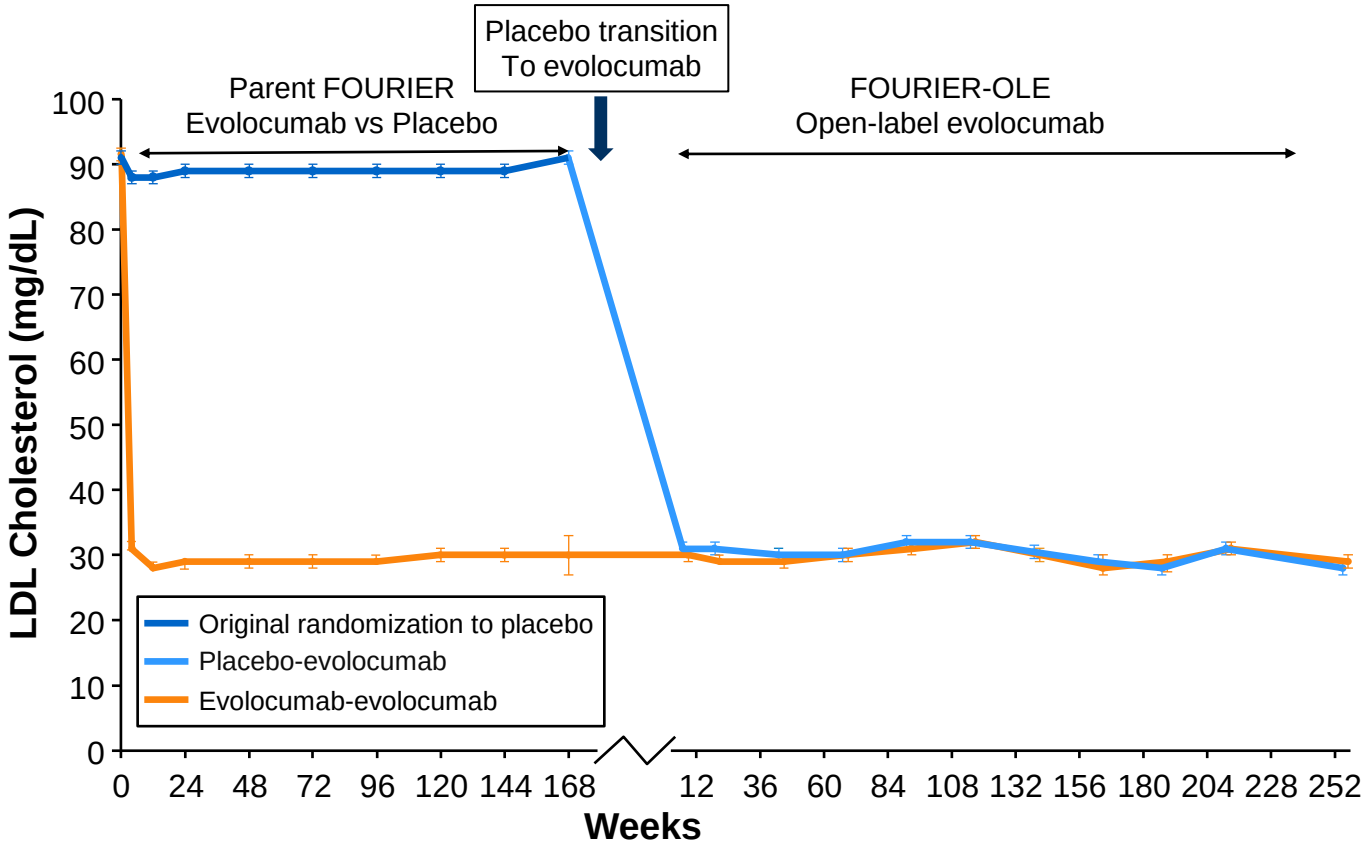


The annual incidence rates of safety events of interest were consistent with the established safety profile

*Data for the parent FOURIER trial are restricted to patients who entered FOURIER-OLE
[a]During parent FOURIER only
[b]Patients with DM at baseline were not at risk for developing new-onset DM
AE = adverse event; DM = diabetes mellitus; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; OLE = open-label extension
O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

FOURIER-OLE Trial

Key Results: Median LDL-C Concentration in Parent FOURIER and FOURIER-OLE Trials



12 weeks into FOURIER-OLE:

- Median LDL-C = 30 mg/dL (IQR: 19–48)
- LSM percentage reduction in LDL-C from baseline with evolocumab = 58.4% (95% CI: 57.6–59.2)
- Consistent LDL-C reduction in patients randomized to evolocumab (median follow-up of 7.1 years)

Error bars represent 95% CI

CI = confidence interval; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; LSM = least-square mean; OLE = open-label extension

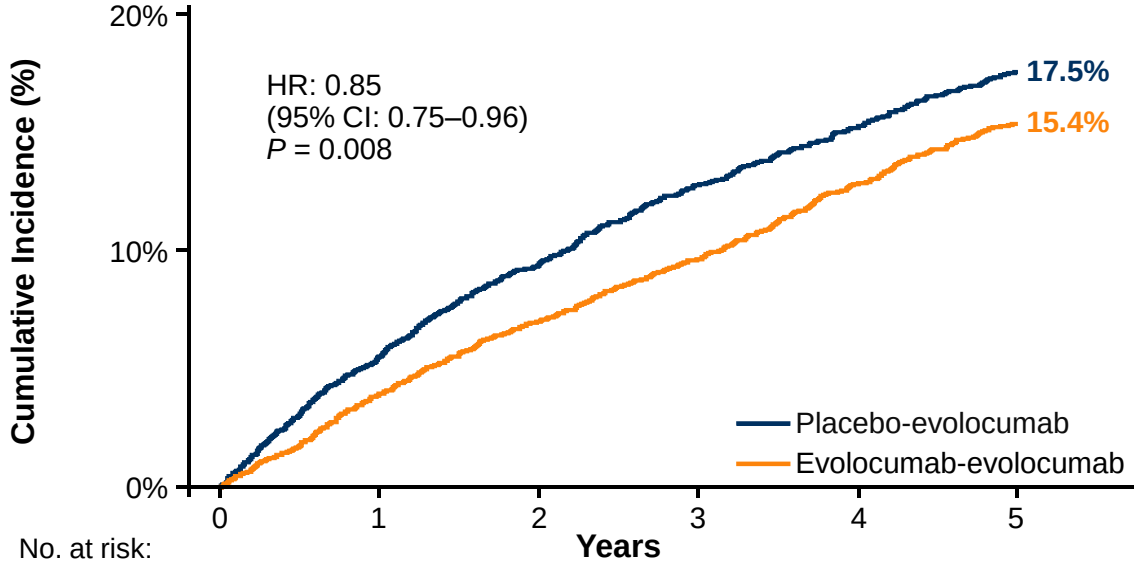
O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

FOURIER-OLE Trial

Key Results: Major Adverse CV Events

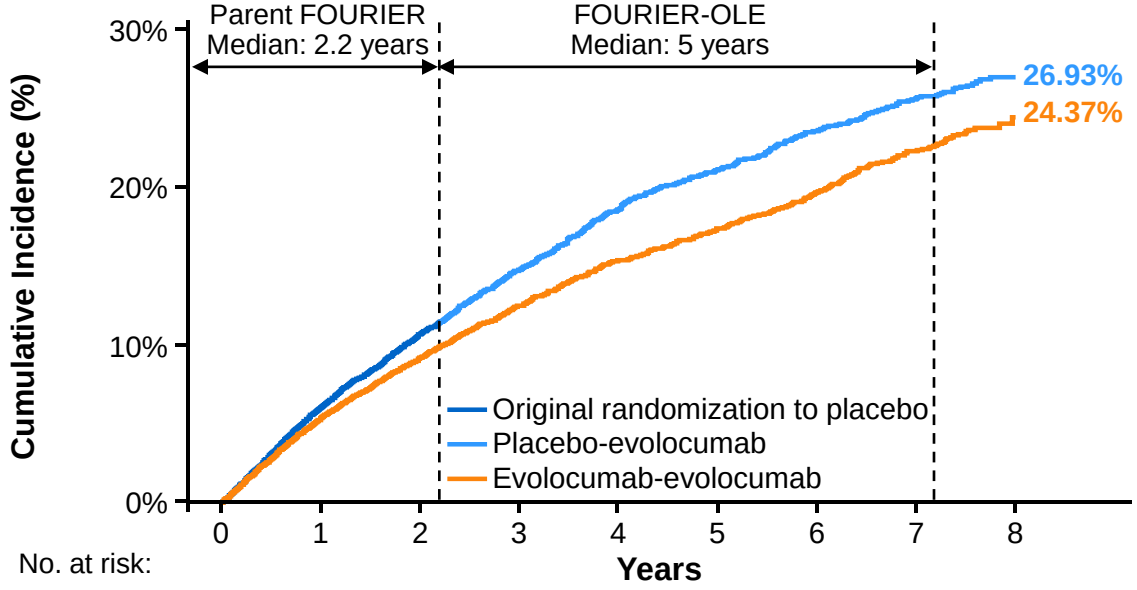
Prespecified Exploratory Analysis (Primary Endpoints) – CV death, MI, stroke, hospitalization for UA, or CoR*

FOURIER-OLE[1]



No. at risk:						
Placebo-evolocumab	3,280	3,055	2,876	2,716	2,573	1,706
Evolocumab-evolocumab	3,355	3,186	3,033	2,890	2,716	1,754

Parent FOURIER + FOURIER-OLE[2]



No. at risk:									
Placebo-evolocumab	13,780	12,822	8,467	3,260	2,654	2,526	2,372	1,498	189
Evolocumab-evolocumab	13,784	12,937	8,683	3,389	2,814	2,699	2,550	1,569	165

During the FOURIER-OLE trial, there was a 15% lower risk of the primary endpoint in patients originally randomized in the parent trial to evolocumab than patients originally randomized in the parent trial to placebo.

*Limitations to the FOURIER-OLE include but are not limited to: all patients in the extension program were treated with open-label evolocumab resulting in no concurrent placebo arm during this period; cardiovascular outcomes were prespecified for the current analysis, but considered exploratory; *P* values are nominal and not adjusted for multiplicity[1]

CI = confidence interval; CoR = coronary revascularization; CV = cardiovascular; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; HR = hazard ratio; MI = myocardial infarction; OLE = open-label extension; UA = unstable angina

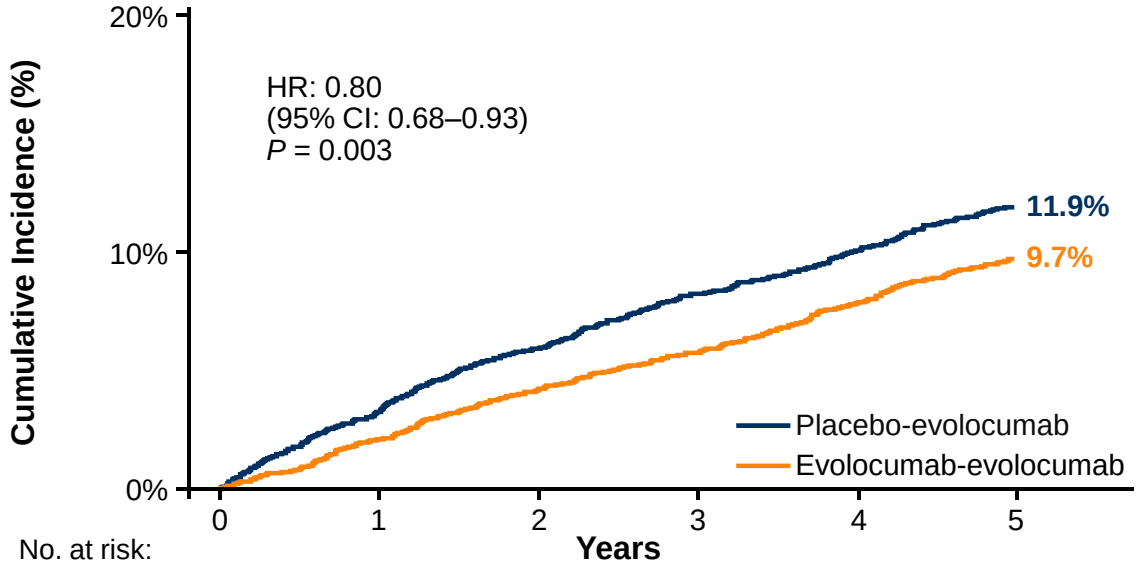
1. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119. 2. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119; supplementary material.

FOURIER-OLE Trial

Key Results: Major Adverse CV Events

Prespecified Exploratory Analysis (Secondary Endpoints) – CV death, MI, or stroke*

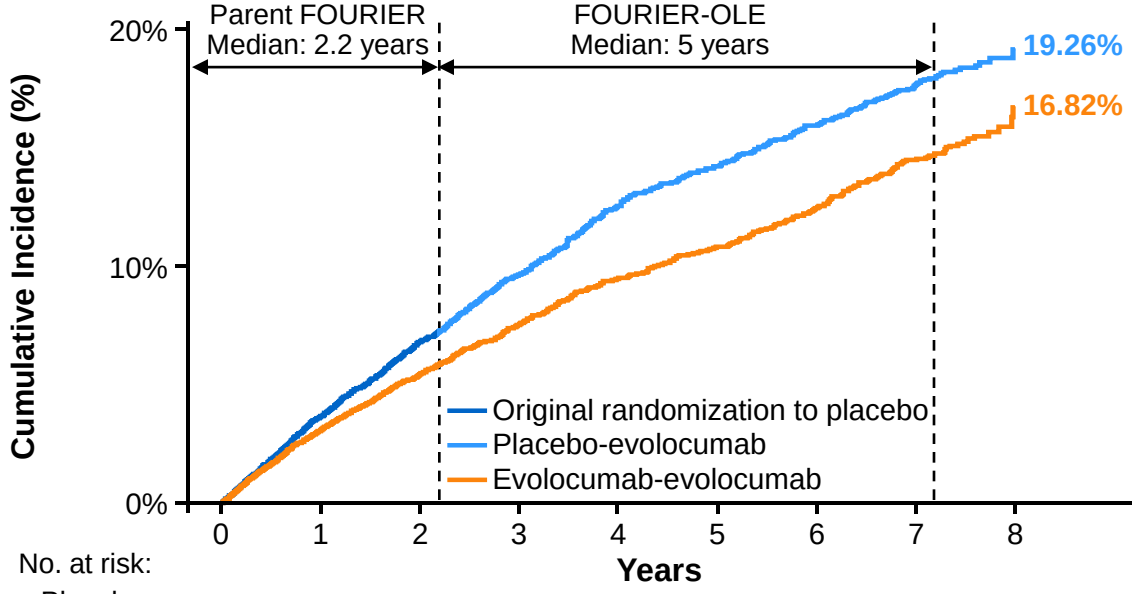
FOURIER-OLE[1]



No. at risk:

Placebo-evolocumab	3,280	3,128	2,987	2,857	2,729	1,809
Evolocumab-evolocumab	3,355	3,247	3,123	3,012	2,870	1,862

Parent FOURIER + FOURIER-OLE[2]



No. at risk:

Placebo-evolocumab	13,780	13,140	8,846	3,470	2,861	2,757	2,621	1,664	216
Evolocumab-evolocumab	13,784	13,240	9,051	3,617	3,046	2,946	2,810	1,746	185

During the FOURIER-OLE trial, there was a 20% lower risk of the key secondary endpoint in patients originally randomized in the parent trial to evolocumab than patients originally randomized in the parent trial to placebo.

*Limitations to the FOURIER-OLE include but are not limited to: all patients in the extension program were treated with open-label evolocumab resulting in no concurrent placebo arm during this period; cardiovascular outcomes were prespecified for the current analysis, but considered exploratory; *P* values are nominal and not adjusted for multiplicity[1]

CI = confidence interval; CV = cardiovascular; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; HR = hazard ratio; MI = myocardial infarction; OLE = open-label extension

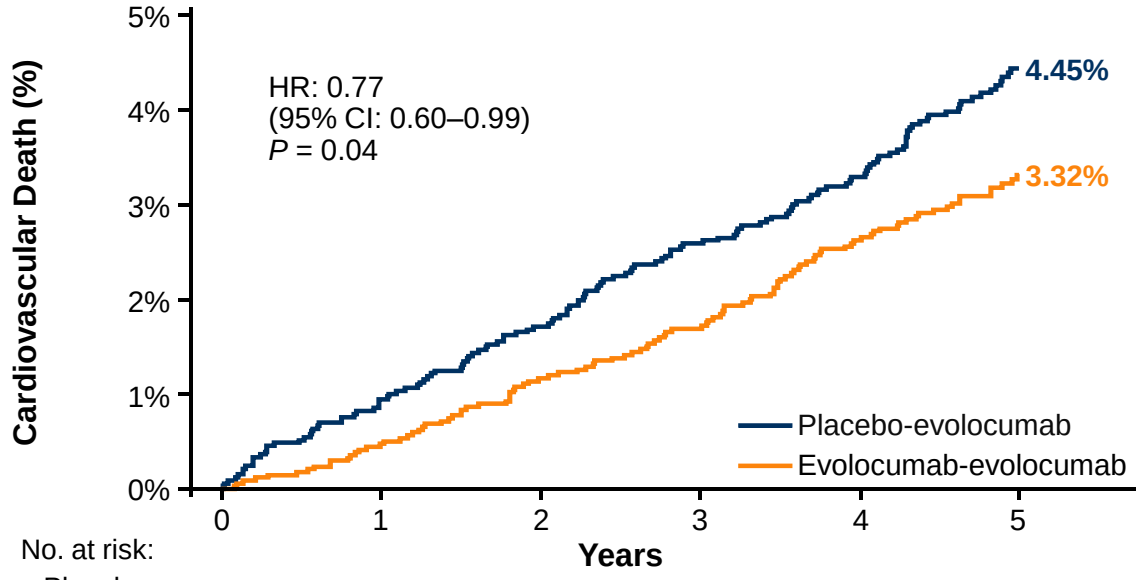
1. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119. 2. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119; supplementary material.

FOURIER-OLE Trial

Key Results: Major Adverse CV Events

Prespecified Exploratory Analysis (CV death)*

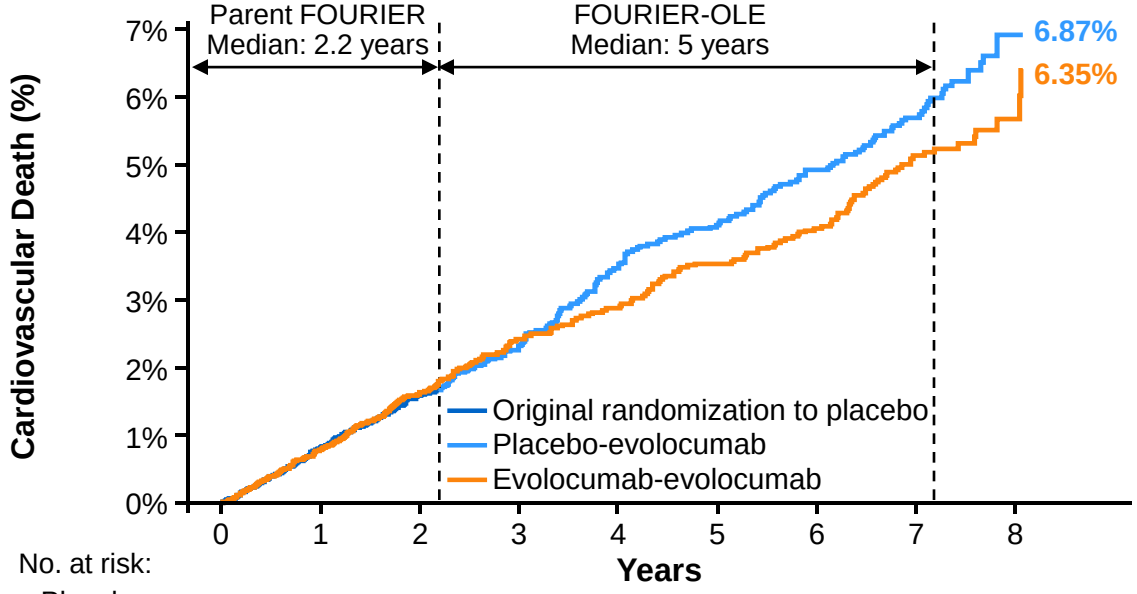
FOURIER-OLE[1]



No. at risk:

Placebo-evolocumab	3,280	3,223	3,155	3,081	2,991	2,049
Evolocumab-evolocumab	3,355	3,314	3,244	3,173	3,080	2,069

Parent FOURIER + FOURIER-OLE[2]



No. at risk:

Placebo-evolocumab	13,780	13,590	9,399	3,753	3,167	3,098	2,996	1,965	268
Evolocumab-evolocumab	13,784	13,598	9,464	3,826	3,270	3,204	3,109	1,988	237

During the FOURIER-OLE trial, there a 23% lower risk of cardiovascular death in patients originally randomized in the parent trial to evolocumab than patients originally randomized in the parent trial to placebo.

*Limitations to the FOURIER-OLE include but are not limited to: all patients in the extension program were treated with open-label evolocumab resulting in no concurrent placebo arm during this period; cardiovascular outcomes were prespecified for the current analysis, but considered exploratory; *P* values are nominal and not adjusted for multiplicity[1]

CI = confidence interval; CV = cardiovascular; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; HR = hazard ratio; OLE = open-label extension

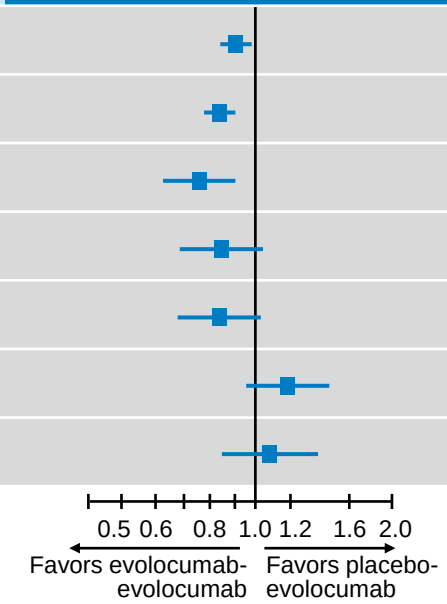
1. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119. 2. O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119; supplementary material.

FOURIER-OLE Trial

Key Results: Major Adverse CV Events (1/2)

First Occurrence of Prespecified Exploratory Analysis (Primary Endpoints) – CV Death, MI, Stroke, Hospitalization for UA, or CoR for the Parent FOURIER and FOURIER-OLE Population*

	Primary endpoint	Incidence rates (%) Evolocumab-evolocumab	Incidence rates (%) Placebo-evolocumab	HR (95% CI)
FOURIER	Year 1	5.46	6.20	0.88 (0.80–0.97)
FOURIER	Year 2+	4.46	5.52	0.81 (0.73–0.89)
FOURIER-OLE	Year 1	4.04	5.70	0.71 (0.57–0.89)
FOURIER-OLE	Year 2	3.68	4.52	0.81 (0.63–1.04)
FOURIER-OLE	Year 3	3.36	4.21	0.80 (0.62–1.03)
FOURIER-OLE	Year 4	4.44	3.65	1.21 (0.94–1.56)
FOURIER-OLE	Year 5+	3.67	3.48	1.06 (0.80–1.40)



*Limitations to the FOURIER-OLE include but are not limited to: all patients in the extension program were treated with open-label evolocumab resulting in no concurrent placebo arm during this period; cardiovascular outcomes were prespecified for the current analysis, but considered exploratory; *P* values are nominal and not adjusted for multiplicity

CI = confidence interval; CoR = coronary revascularization; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; HR = hazard ratio; OLE = open-label extension

O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

FOURIER-OLE Trial
Conclusion (1/2)

- The FOURIER-OLE trial has **the longest follow-up** to date on a PCSK9i
- Baseline median LDL-C at the end of the parent FOURIER trial:
  - In patients originally randomized to evolocumab**, reduction in LDL-C was consistent over long-term follow-up**
- Evolocumab demonstrated both **safety and tolerability** through long-term follow-up:
  - Median follow-up of 5 years and maximum exposure times of more than 8 years when FOURIER and FOURIER-OLE trials were combined
  - Long-term follow-up reported **no increase in the frequency of AEs**
- At 12 weeks after the start of the FOURIER-OLE trial,
  - Median **LDL-C → 30 mg/dL** (IQR: 19–48) → **reduced the risk of MACE by 15%–20%**
  - Percentage reduction* in **LDL-C** from baseline with evolocumab → **58.4%**
  - 63% of patients achieved LDL-C levels < 40 mg/dL

*Least-square mean percentage reduction at 12 weeks
AE = adverse event; CV = cardiovascular; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MI = myocardial infarction; OLE = open-label extension; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor
O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

FOURIER-OLE Trial
Conclusion (2/2)

- **Legacy effect** was evidenced by subsequent continued accrual of CV benefit over several years, irrespective of patients' randomization assignment in the parent FOURIER trial
  - LDL-C levels remained similar in the original two treatment arms during the FOURIER-OLE trial
- **Evolocumab-evolocumab group exhibited lower rate of MACE**, including CV death
- The FOURIER-OLE trial reported no noncardiovascular or all-cause mortality event(s)
- Continued divergence in the risk of MACE reflects both **the legacy effect and the lag in the onset of clinical benefit** from the placebo patients transitioned to evolocumab in the FOURIER-OLE trial
- **Early initiation** of evolocumab and continued **LDL-C reduction** maximize **clinical benefit** in patients with ASCVD

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; FOURIER = Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; OLE = open-label extension

O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.