Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR040.0226	**CARDIOVASCULAR AGENTS** **NEXLETOL** (bempedoic acid tablet) **NEXLIZET** (bempedoic acid/ezetimibe tablet)
Effective Date: 4/1/2026	**Review/Revised Date**: 07/20, 05/21, 05/22, 05/23, 05/24, 05/25, 02/26 (snm)
Original Effective Date: 08/20	**P&T Committee Meeting Date**: 06/20, 10/20, 06/21, 06/22, 06/23, 06/24, 06/25, 02/26
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For **all** requests, all of the following must be met:

1. The requested medication is being used for one of the following indications:
    a. Established **clinical atherosclerotic cardiovascular disease (ASCVD)** as defined as one or more of the following:
        i. Acute coronary syndromes
        ii. History of myocardial infarction
        iii. Stable/unstable angina
        iv. Coronary or other arterial revascularization
        v. Stroke or transient ischemic attack
        vi. Peripheral arterial disease presumed to be of atherosclerotic origin
        vii. Clinically significant coronary heart disease of atherosclerotic origin identified by diagnostic catheterization, imaging (CT angiogram or cardiac MRI), or stress testing (nuclear stress test or stress echocardiogram)
    b. **Primary prevention of ASCVD** in patients who are at high risk of cardiovascular disease (e.g., diagnosis of diabetes mellitus in patients greater than 60 years old or high 10-year ASCVD risk indicated by a clinical risk estimator – see appendix)

   c. Confirmed diagnosis **familial hypercholesterolemia (FH)** based on one of the following:
      i. A "possible" or "definite" diagnosis of FH via Simon Broome criteria **OR** a "probable" or "certain" diagnosis of FH via Dutch Lipid Clinic Network Criteria score of greater than or equal to 6 (see appendix)
      ii. Genetic mutation in one of the following genes: low-density lipoprotein receptors (LDLR), apolipoprotein B gene (APOB), or proprotein convertase subtilisin kexin type 9 (PCSK9), or ARH adaptor protein 1 (LDLRAP1)
      iii. LDL-C greater than 190 mg/dL (pretreatment or highest level while on treatment) and secondary causes have been ruled out. Secondary causes may include hypothyroidism, nephrosis, or extreme dietary patterns
2. Presence of xanthomas
   One of the following
   a. **For clinical ASCVD or FH:** fasting LDL-C equal to or greater than 70 mg/dL despite treatment with therapies below
   b. **For primary prevention of ASCVD:** fasting LDL-C equal to or greater than 100 mg/dL despite treatment with therapies below
3. One of the following:
   a. Current use of high-intensity statin therapy for at least three months (e.g., atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily)
   b. Provider attestation of statin intolerance, defined as one of the following:
      i. Rhabdomyolysis
      ii. Skeletal muscle related symptoms while receiving separate trials of at least two different statins with resolution of symptoms after discontinuation
      iii. Elevated liver enzymes while on separate trials of at least two different statins with resolution after discontinuation
   c. The patient has an FDA labeled contraindication to a statin
4. Current use of ezetimibe 10 mg daily for at least three months, or documented intolerance/contraindication to its use

For reauthorization:
Documented response to therapy, as defined as a decrease in LDL-C levels from pre-treatment levels

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Approved for adults 18 years of age and older

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization will be approved for one year and reauthorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

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Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Bempedoic acid is a lipid-lowering medication with a novel mechanism of action. Bempedoic acid is a prodrug converted to its active metabolite by very long-chain acyl-CoA synthetase 1 (ACSVL1), an enzyme found primarily in the liver. Following activation the agent inhibits adenosine triphosphate-citrate lyase (ACL), an enzyme two steps upstream of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. This results in decreased cholesterol synthesis and lower serum LDL-C levels.

Warnings and precautions include hyperuricemia and tendon rupture

- In clinical trials bempedoic acid increased the rate of hyperuricemia and development of gout. The risk for gout events was higher in patients with a prior history of gout. The manufacturer recommends monitoring serum uric acid when clinically indicated and initiating urate-lowering medications if appropriate.
- Bempedoic acid has also been associated with an increased risk of tendon rupture in clinical trials. Ruptures involved the rotator cuff, biceps tendon, and Achilles tendon. Manufacturer recommendations include: consideration of alternative therapy in patients with a history of tendon disorder/rupture, discontinuation of therapy with tendon rupture, joint pain, swelling, inflammation.

- Most common adverse events for bempedoic acid (incidence of ≥ 2% and at a higher frequency than placebo) were upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain/discomfort, bronchitis, pain in extremity, anemia, renal impairment, gout, cholelithiasis and elevated liver enzymes.

FDA APPROVED INDICATIONS:

- To reduce the risk of major adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke, or coronary revascularization) in adults at increased risk for these events who are unable to take recommended statin therapy (including those not taking a statin).
- As an adjunct to diet, in combination with other low-density lipoprotein cholesterol (LDL-C) lowering therapies, or alone when concomitant LDL-C lowering therapy is not possible, to reduce LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).

POSITION STATEMENT:

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality globally and in the United States and is defined as acute coronary syndrome, myocardial infarction, angina, stroke, and/or peripheral artery disease.

- Modifiable risk factors associated with the development of ASCVD include: Suboptimal diet, inactivity, obesity, diabetes, hypertension, tobacco use, and high blood cholesterol.
- Serum cholesterol levels are known to be related to ASCVD. Although LDL-C is the dominant form of atherogenic cholesterol, VLDL-C is also atherogenic. The combination of LDL-C and VLDL-C is referred to as non-HDL-C. The predominant protein embedded in both LDL-C and VLDL-C is apolipoprotein-B. Both non-HDL-C and apolipoprotein-B have been shown to be stronger predictors of atherogenicity than LDL-C alone.
- C-reactive protein (CRP) is a biomarker indicative of inflammation that has also been associated with increased risk of ASCVD.
  In clinical trials of cholesterol-lowering medications, reducing LDL-C levels has been shown to markedly reduce ASCVD. For this reason, clinical practice guidelines for the prevention of cardiovascular events associated with ASCVD utilize LDL levels as the primary measure of medication efficacy.

Clinical Practice Guidelines

2022 American College of Cardiology expert consensus decision pathway on the role of nonstatin therapy[21]

2022 American College of Cardiology expert consensus decision pathway for integrating atherosclerotic cardiovascular disease and multimorbidity treatment: a

framework for pragmatic, patient-centered care: a report of the American College of Cardiology Solution Set Oversight Committee[22]

2019 American College of Cardiology/American Heart Association (ACC/AHA) guideline on the primary prevention of cardiovascular disease[6]

2018 ACC/AHA Guideline on the management of blood cholesterol[7]

Summary of Recommendations:

- Atherosclerotic cardiovascular disease (ASCVD) was originally defined in 2018 to include: acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.[7]
- In 2022 this definition was amended to also include coronary heart disease with or without revascularization.[22] Per the NIH National Heart, Lung, and Blood institute, coronary heart disease is defined as a type of heart disease that occurs when the arteries of the heart cannot deliver enough oxygen-rich blood to the heart muscle due to narrowing from the buildup of fatty deposits called plaques. It is also known as coronary artery disease or ischemic heart disease.
- HMG-CoA reductase inhibitors (statins) are the cornerstone of lipid-lowering therapy and recommended for patients with clinical ASCVD, or at least moderate risk for developing ASCVD. High-intensity statins can lower LDL-C levels by >50%.
- Ezetimibe is the most commonly-used non-statin agent. It is generally well tolerated and has been shown to lower LDL-C levels by 13-20% in clinical trials. Ezetimibe is guideline-recommended for patients with clinical ASCVD at high risk for cardiovascular events and LDL-C ≥70mg/dL despite maximally-tolerated statin therapy.
- PCSK9 inhibitors are highly effective LDL-lowering medications that consistently reduced LDL-C by >50% in clinical trials. These medications are also generally well tolerated. PCSK9 inhibitors are guideline-recommended for patients with clinical ASCVD, very high risk for cardiovascular events, and LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL despite maximally tolerated statin AND ezetimibe therapy.
- Ezetimibe is preferred over PCSK9 inhibitors in the population outlined above d/t higher availability of long-term safety evidence for ezetimibe, and the low cost-value of the PCSK9 inhibitors.
- For patients with clinical ASCVD at very high risk on a statin therapy for secondary prevention require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial nonstatin therapy.

- At the time of publication (2022) there were no outcome studies for bempedoic acid and therefore it was recommended as third-line nonstatin therapy behind ezetimibe and PCSK9 monoclonal antibodies.
- Bile-acid sequestrants are also effective for reducing LDL-C, but are often poorly tolerated d/t gastrointestinal adverse effects and can cause hypertriglyceridemia. They are guideline-recommended as a third-line alternative to the above agents.
- Several triglyceride-lowering medications, Niacin and the fibrates, also offer a modest LDL-reduction, but have not been shown to reduce ASCVD when added-on to statin therapy. Clinical practice guidelines do not consider these agents among the LDL-lowering medications for ASCVD risk reduction.

Clinical Trials for bempedoic acid:

Cardiovascular outcome trials

CLEAR-Outcomes[18] was the first bempedoic acid study evaluating CV outcomes. In adults with a history of ASCVD or at high-risk for a CV event who cannot tolerate more than a low dose of a statin, bempedoic acid significantly reduced the risk of composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization compared to placebo [11.7% versus 13.3%; absolute risk reduction (ARR) 1.6%; number needed to treat (NNT) 63 over 3.4 years; p =0.004]. A subgroup analysis of primary prevention participants (n = 4206) has also been published[19].

- Study Design: Randomized, double-blind, placebo controlled, 42 weeks duration
- Intervention: bempedoic acid 180mg once daily (n = 6992) or a matched placebo (n = 6978)
- Patient population: statin intolerant adults at high risk of a CVD event
    - Key inclusion: statin intolerant (lower dose statins were allowed, i.e., average daily dose of rosuvastatin < 5 mg, atorvastatin <10 mg), fasting LDL ≥ 100 mg/dL, history of or at high risk for CVD
        - High risk for CVD criteria:
            - Patients with type 1 or type 2 diabetes, aged >65 years (women) or >60 years (men)
            - Coronary artery calcium score >400 Agatston units
            - Reynolds Risk score >30% or a SCORE Risk score >7.5% over 10 years*
    - Baseline demographics: 70% established CVD, 46% diabetes, 23% on statin, 12% ezetimibe, means – 66 years, BMI 30, LDL 140, median hsCRP 2.3 mg/L
- Primary endpoint: composite of nonfatal MI, nonfatal stroke, coronary revascularization or death from CV causes
    - 819 patients (11.7%) in the bempedoic acid group and in 927 patients (13.3%) in the placebo group (hazard ratio, 0.87; 95% CI, 0.79 to 0.96; P=0.004)

  - ARR 1.6%, NNT 63 over 3.4 years
- Secondary endpoints:
  - Fatal or nonfatal MI (3.7% versus 4.8%; ARR = 1.1%; NNT = 91; p = 0.002)
  - Coronary revascularization (6.2% versus 4.8%; ARR = 1.42%; NNT= 72; p = 0.001)
  - Fatal or nonfatal stroke, death from cardiovascular cause and death from any cause were not statistically different

* 10-year risk of a CV event. Reynolds risk and SCORE risk scores are based on sex, age, smoking status, systolic BP, high sensitivity C-reactive protein (hsCRP), familial history of CVD events, total and HDL cholesterol, LDL cholesterol (SCORE only.

Subgroup analysis of primary prevention participants
- Baseline demographics: 66% diabetes, 19% on statin, 8% ezetimibe, means – 68 years, BMI 30, LDL 142, median hsCRP 2.4 mg/L
- Primary endpoint: 111 events (5.3%) in the bempedoic acid group and 161 events (7.6%) in the placebo group; (hazard ratio 0.70; 95% CI, 0.55-0.89; P = 0.002)
  - ARR 2.3%, NNT 43

<u>Primary hyperlipidemia trials</u>
Both efficacy trials required individuals to have HeFH or established CVD.
Kausik et al. (PubMed ID #30865796)
- Study Design: Randomized, double-blind, placebo controlled, phase 3 clinical trial
- Study Duration: 52 weeks for safety, 12 weeks for efficacy
- Patient population: Adults (n=2230) with ASCVD, HeFH, or both and a fasting LDL-C level of ≥70mg/dL despite maximally tolerated statin therapy.
  - Diagnosis of HeFH was made either by genotyping or using the Dutch Lipid Clinical Network Criteria with a score >8 or a Simon Broome assessment of “definite” HeFH.
  - Diagnosis of ASCVD included MI, silent MI, unstable angina, coronary revascularization procedures, or clinically significant CHD diagnosed by invasive or noninvasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging)
  - Clinically significant exclusion criteria: Baseline triglyceride (TG) level of ≥500 mg/dL, HbA_{1c} ≥10%, body mass index (BMI) ≥50 kg/m^2, concomitant use of simvastatin dosed at >40 mg daily, gemfibrozil, a PCSK9 inhibitor, or any other experimental medication, cardiac event in the last 3 months
- Intervention: Patients were randomized in a 2:1 ratio to receive bempedoic acid 180mg once daily or a matched placebo.

- Endpoints:
  - Primary endpoint: Overall safety. Defined as incidence of adverse events and changes in safety laboratory values (AST, ALT, CK, SCr)
  - Principal secondary endpoint: Percentage change in LDL-C from baseline to week 12
  - Key secondary endpoints:
    - Percentage change in non-high-density lipoprotein (non-HDL) cholesterol, total cholesterol, apolipoprotein B, and CRP from baseline to week 12
- Results:
  - Primary Outcomes (Safety):

Outcome	**Bempedoic Acid** n=1487	**Placebo** n=742	**P-value**
Any adverse event	1167 (78.5%)	584 (78.7%)	0.91
Serious adverse event	216 (14.5%)	104 (14.0%)	0.80
Adverse event leading to discontinuation of trial agent	162 (10.9%)	53 (7.1%)	0.005
Major adverse cardiac event	68 (4.6%)	42 (5.7%)	0.30
Myalgia	89 (6.0%)	45 (6.1%)	0.92
New-onset or worsening DM	49 (3.3%)	40 (5.4%)	0.02
Gout	18 (1.2%)	2 (0.3%)	0.03
Change from baseline serum uric acid level (± SD)	+0.73 ± 1.11mg/dl	-0.06 ± 0.87mg/dl	<0.001

  - Secondary Outcomes (Efficacy):

Outcome	**Bempedoic Acid** n=1487	**Placebo** n=742	**Mean difference (95% CI)**	**P-value**
Change in LDL-C at 12 weeks	-16.5%	1.6%	-18.1% (-20.0 to -16.1)	<0.001
change in non-HDL-C at 12 weeks	-11.9%	1.5%	-13.3% (-15.1 to -11.6)	<0.001
Change in total C at 12 weeks	-10.3%	0.8%	-11.1% (-12.5 to -9.8)	<0.001
Change in apolipoprotein B at 12 weeks	-8.6%	3.3%	-11.9% (-13.6 to -10.2)	<0.001
Change in CRP at 12 weeks*	-22.4%	2.6%	-21.5% (-27.0 to -16.0)	<0.001

*CRP results are reported as median.

- GRADE evidence rating: B

- Strengths: Large sample size and study duration for detecting adverse events; high internal validity. Population on maximally tolerated statin therapy is indicated for additional lipid-lowering therapy.
- Limitations: Short duration for efficacy (12-weeks), few patients had comorbid diabetes, and patients with suboptimal control were excluded; surrogate lab values utilized as efficacy endpoints

Goldberg et al. (PubMed ID # 31714986)

- Study Design: Randomized, double-blind, placebo-controlled, phase 3 clinical trial
- Study Duration: 52 weeks
- Patient population: Adults (n=779) with ASCVD, HeFH, or both and a fasting LDL-C level of ≥70mg/dL despite maximally tolerated statin therapy.
  - Clinically relevant exclusion criteria: baseline triglyceride (TG) level of ≥500 mg/dL, HbA_{1c} ≥10%, Body mass index (BMI) ≥50 kg/m^2, cardiac event in the last 3 months
- Intervention: Patients were randomized in a 2:1 ratio to receive bempedoic acid 180 mg once daily or a matched placebo.
- Primary endpoint: Percent change in LDL-C from baseline to week 12
  - Secondary endpoints:
    - Percent change in LDL-C from baseline to week 24
    - Percentage change from baseline to weeks 12 and 24 for: non-HDL-C, total-C, apolipoprotein B, and CRP
- Results:
  - Efficacy:

	Bempedoic Acid (n=522)	Placebo (n=257)	Mean difference (95% CI)	P-value
LDL-C				
Percent change at 12 weeks (Primary Outcome)	-15.1%	2.4%	-17.4% (-21.0 to -13.9)	<0.001
Percent change at 24 weeks	-12.1%	2.7%	-14.8% (-19.5 to -10.0)	<0.001
Non-HDL-C				
Percent change at 12 weeks	-10.8%	2.3%	-13.0% (-16.3 to -9.8)	<0.001
Percent change at 24 weeks	-10.2%	2.4%	-12.6% (-16.6 to -8.7)	<0.001
Total-C				
Percent change at 12 weeks	-9.9%	1.3%	-11.2% (-13.6 to -8.8)	<0.001
Percent change at 24 weeks	-9.3%	1.5%	-10.8% (-13.7 to -7.8)	<0.001
Apolipoprotein B				
Percent change at 12 weeks	-9.3%	1.3%	-13.0% (-16.1 to -9.9)	<0.001
Percent change at 24 weeks	-8.6%	4.4%	-13.0% (-17.8 to -8.2)	<0.001
CRP*				
Percent change at 12 weeks	-18.7%	-9.4%	-8.7% (-17.2 to -0.4)	0.04
Percent change at 24 weeks	-24.1%	1.6%	-21.3% (-32.3 to -10.0)	<0.001

*CRP results are reported as median

  - Safety:

    - The occurrence of any adverse event was more common in the placebo group (70.8 vs 70.1%), but more patients in the treatment group discontinued therapy due to adverse events (10.9 vs 8.6%)
    - Adverse evets leading to discontinuation that occurred in >0.5% of patients and were more common in the treatment group than placebo: myalgia (1.0 vs 0.8%), increased AST (0.6 vs 0%), arthralgia (0.6 vs 0%), muscle spasms (0.6 vs 0%).
    - Other adverse events of note (bempedoic acid vs placebo): myalgia (2.9 vs 3.1%), muscle spasm (2.1 vs 1.2%), increased uric acid (2.7 vs 0.4%), gout (2.1 vs 0.8%), increased SCr (0.8 vs 0.4%)
- GRADE evidence rating: B
    - Strengths: High internal validity. Population on maximally tolerated statin therapy, and required alternative lipid lowering therapy to be considered. Included all other lipid-lowering options.
    - Limitations: 4 week run-in period with required adherence for randomization; results can be extrapolated to highly adherent patients only. Few patients had concomitant DM, and patients with suboptimal control of DM were excluded. Surrogate lab values utilized as efficacy endpoints rather than clinically relevant consequences of atherosclerosis.

Ballantyne et al. (PubMed ID #31357887)

- Study Design: Randomized, double-blind, phase 3 clinical trial. Participants were randomized into 4 groups: bempedoic acid + ezetimibe, bempedoic acid alone, ezetimibe alone, or placebo.
- Study Duration: 12 weeks
- Patient population: Adults (n=382) with ASCVD, HeFH, or multiple ASCVD risk factors with elevated LDL-C despite maximally tolerated statin therapy.
    - Exclusion criteria: baseline triglyceride (TG) level of ≥500 mg/dL, Body mass index (BMI) ≥40 kg/m^2, cardiac or cerebrovascular event in the last 3 months
- Intervention: Patients were randomized in a 2:2:2:1 ratio to the following 4 groups, respectively: 1) bempedoic acid 180mg + ezetimibe 10mg, 2) bempedoic acid 180mg, 3) ezetimibe 10mg, 4) placebo
- Primary endpoint: Percent change in LDL-C from baseline to week 12
    - Secondary endpoints:
        - Percentage change from baseline to week 12 for: non-HDL-C, total-C, apolipoprotein B, and CRP
    - The bempedoic acid 180mg + ezetimibe 10mg group was compared to all other groups, but no other groups were compared directly (i.e.: bempedoic acid alone was not directly compared to ezetimibe alone)
- Results:
    - Efficacy:

	Bempedoic Acid + Ezetimibe (n=86)	Bempedoic Acid (n=88)	Ezetimibe (n=86)	Placebo (n=41)	P-value Combination therapy vs. Other Groups
LDL-C Percent change at 12 weeks (Primary Outcome)	-36.2%	-17.2%	-23.2%	1.8%	<0.001 for all comparisons
Non-HDL-C Percent change at 12 weeks	-31.9%	-14.1%	-19.9%	1.8%	<0.001 for all comparisons
Total-C Percent change at 12 weeks	-26.4%	-12.1%	-16.0%	0.7%	<0.001 for all comparisons
Apolipoprotein B Percent change at 12 weeks	-24.6%	-11.8%	-15.3%	5.5%	0.003 for ezetimibe <0.001 for other comparisons
CRP Percent change at 12 weeks	-35.1%	-31.9%	-8.2%	21.6%	NS for bempedoic acid 0.002 for ezetimibe <0.001 for placebo

  - Safety:
    - The occurrence of any adverse event was more common in the bempedoic acid + ezetimibe group than the placebo group (62.4% vs 43.9%).
    - No serious/fatal AE's occurred in any group.
    - The most common AE's reported in the bempedoic acid + ezetimibe group were: blood uric acid increase, constipation, fatigue, muscle spasms and oral discomfort. Each of these AE's occurred in 2 patients (2.4%).
    - AE's leading to treatment discontinuation were similar between groups receiving active treatment, and higher than placebo (bempedoic acid/ezetimibe = 8.2%, bempedoic acid = 10.2%, ezetimibe = 11.6%, placebo = 4.9%).
- GRADE evidence rating: C
  - Strengths: active comparator, higher proportion of patients than previous trials had comorbid diabetes, population on maximally tolerated statin therapy
  - Limitations: All other lipid-lowering therapies outside of trial medications were excluded. Short trial duration is unlikely to reveal less common adverse effects. Surrogate lab values utilized as efficacy endpoints rather than clinically relevant consequences of atherosclerosis.

APPENDIX: Diagnostic Scoring Tools for familial hypercholesterolemia

World Health Organization (WHO)/Dutch Lipid Network criteria

Family history			
a	First degree relative known with premature (men<55 yrs, women <60yrs) coronary and vascular disease.		1
b	First degree relative known with LDL-cholesterol >95th percentile.		
	and/or		
a	First degree relative with tendon xanthomata and/or arcus cornealis.		2
b	Children below 18 yrs. with LDL-cholesterol >95th percentile.		
Clinical history			
a	Patient has premature (men<55 yrs, women <60yrs) CAD		2
b	Patient has premature (men<55 yrs, women <60yrs) cerebral or peripheral vascular disease.		1
Physical examination			
a	Tendon xanthomata		6
b	Arcus cornealis below the age of 45 yrs.		4
Laboratory analysis			
		mmol/l	mg/dl
a	LDL-cholesterol >8.5	>330	8
b	LDL-cholesterol 6.5 - 8.4	250-329	5
c	LDL-cholesterol 5.0 - 6.4	190-249	3
d	LDL-cholesterol 4.0 - 4.9	155-189	1
	(HDL-cholesterol and triglycerides are normal)		
DNA-analysis			
a	Functional mutation low-density lipoprotein receptor gene present		8

Diagnosis of FH is:	
certain when	>8 points
probable when	6-8 points
possible when	3-5 points

Simon Broome criteria for FH

Diagnose a person with <u>definite</u> familial hypercholesterolemia (FH) if they have:

- Cholesterol concentrations as defined in table 1 and tendon xanthomas, or evidence of these signs in first- or second-degree relative

OR

- Deoxyribonucleic acid (DNA)-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Diagnose a person with <u>possible</u> FH if they have cholesterol concentrations as defined in table 1 and at least one of the following.

- Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative.

- Family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative or greater than 6.7 mmol/l in child, brother or sister aged younger than 16 years.

Table 1. Cholesterol levels to be used as diagnostic criteria for the index individual levels either pre-treatment or highest on treatment

	Total cholesterol	LDL-C
Child/young person	> 6.7 mmol/L (260 mg/dL)	> 4.0 mmol/L (154 mg/dL)
Adults	> 7.5 mmol/L (290 mg/dL)	> 4.9 mmol/L (190 mg/dL)

ASCVD Risk Estimators:

ACC ASCVD Risk Estimator Plus: https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

Reynolds Risk Score: https://www.scymed.com/en/smnxph/phqgg440.htm and https://reference.medscape.com/calculator/192/reynolds-cad-risk

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