SUPPLEMENTAL MATERIAL

Table S1. Summary of Major US Guidelines/Consensus Statements for Individuals with DM

Recommendation source	Recommendations
ADA 2017 guidelines[1]	High-intensity statin therapy in addition to lifestyle therapy is recommended for: • Patients of all ages with DM and ASCVD • Patients 40–75 years of age with DM and ASCVD risk factors* Moderate-intensity statin therapy is recommended in patients ≥40 years of age without cardiovascular risk factors. Moderate- or high-intensity statin therapy is recommended for adults with DM who are <40 or >75 years of age with ASCVD risk factors* The addition of ezetimibe to moderate-intensity statin therapy is recommended in: • Patients ≥40 years of age with DM with acute coronary syndrome and LDL-C ≥50 mg/dL (1.3 mmol/L) • Patients with a history of ASCVD who cannot tolerate high-dose statins.
ACC/AHA 2013 guidelines[2]	Primary prevention of ASCVD in individuals with DM is one of the major risk groups identified by the ACC/AHA Expert Panel. Moderate-intensity statins are recommended for the primary prevention of ASCVD in individuals with DM and LDL-C 70–189 mg/dL aged 40–75 years. High-intensity statin therapy is reasonable for adults 40–75 years of age with DM with a ≥7.5% estimated 10-year ASCVD risk,† unless contraindicated. In adults with DM, who are <40 or >75 years of age, or with LDL-C <70 mg/dL, the ACC/AHA Expert Panel indicated that it is reasonable to evaluate the potential for ASCVD benefits, and for adverse effects and drug–drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.

AACE/ACE consensus statement[3]	Treatment targets: • LDL-C goal of <55 mg/dL, non-HDL-C goal of <80 mg/dL, and Apo B goal of <70 mg/dL in individuals at extreme ASCVD risk, including those with T2DM and a prior ASCVD event (ie, recognized “clinical ASCVD”) or CKD Stage 3 or 4 • LDL-C goal of <70 mg/dL, non-HDL-C goal of <100 mg/dL, and Apo B goal of <80 mg/dL in individuals at very high ASCVD risk, including those with DM plus one or more additional risk factors • LDL-C goal of <100 mg/dL, non-HDL-C goal of <130 mg/dL, and Apo B goal of <90 mg/dL in individuals at high ASCVD risk, including those with DM with no other risk factors.
NLA 2016 annual summary[4]	Co-primary treatment target: • LDL-C goal of <70 mg/dL and non-HDL-C goal of <100 mg/dL in individuals at very high ASCVD risk, including those with clinical evidence of ASCVD and/or DM plus ≥2 major ASCVD risk factors or evidence of end-organ damage (eg, retinopathy, microalbuminuria [ACR >30 mg/g], or CKD [eGFR <60 mL/min/1.73 m^2]) • LDL-C goal of <100 mg/dL and non-HDL-C goal of <130 mg/dL in individuals at high ASCVD risk, including patients with ≥3 major ASCVD risk factors; DM with 0 to 1 additional major ASCVD risk factors and no evidence of end-organ damage; CKD Stage 3B or 4; or LDL-C ≥190 mg/dL.

*ASCVD risk factors included LDL-C ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, CKD, albuminuria, and family history of premature ASCVD.

[†]≥7.5% estimated 10-year ASCVD risk included first occurrence of nonfatal myocardial infarction, coronary heart disease death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations.

AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; ACR, albumin-to-creatinine ratio; ADA, American Diabetes Association; AHA, American Heart Association; Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NLA, National Lipid Association; T2, type 2.

Table S2. Summary of Phase 3 Alirocumab ODYSSEY and Evolocumab PROFICIO Studies

	Study acronym, treatment duration, N	Eligibility criteria	Treatment arms	Background statin
ALIROCUMAB Phase 3 ODYSSEY trials				
1	FH I[5] • 78 weeks • N=486	Patients with HeFH, and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or LDL-C ≥100 mg/dL (for patients with no documented ASCVD) Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded	• ALI 75/150 mg Q2W • PBO	Stable maximally tolerated statin* for ≥4 weeks prior to screening ± other LLT
2	FH II[5] • 78 weeks • N=249	Patients with HeFH, and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or LDL-C ≥100 mg/dL (for patients with no documented ASCVD)	• ALI 75/150 mg Q2W • PBO	Stable maximally tolerated statin* for ≥4 weeks prior to screening ± other LLT

		Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded		
3	HIGH FH[6] • 78 weeks • N=107	Patients with HeFH, and LDL-C ≥160 mg/dL Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded	• ALI 150 mg Q2W • PBO	Stable maximally tolerated statin* for ≥4 weeks prior to screening ± other LLT
4	COMBO I[7, 8] • 52 weeks • N=316	Patients with hypercholesterolemia (non-FH), and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or LDL-C ≥100 mg/dL (for patients with no documented ASCVD) Patients with newly diagnosed DM (within 3 calendar months prior to	• ALI 75/150 mg Q2W • PBO	Stable maximally tolerated statin* for ≥4 weeks prior to screening ± other LLT

		randomization) or poorly controlled DM (HbA1c >8.5% at screening) were excluded		
5	COMBO II[8, 9] • 104 weeks • N=720	Patients with hypercholesterolemia (non-FH), and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or LDL-C ≥100 mg/dL (for patients with no documented ASCVD) Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded	• ALI 75/150 mg Q2W • EZE	Stable maximally tolerated statin* for ≥4 weeks prior to screening without other LLT
6	LONG TERM[10] • 78 weeks • N=2341	Patients with HeFH or non-FH, and LDL-C ≥70 mg/dL No specified DM exclusion criteria	• ALI 150 mg Q2W • PBO	Stable maximally tolerated statin* for ≥4 weeks prior to screening ± other LLT
7	OPTIONS I[11, 12] • 24 weeks	Patients with HeFH or non-FH, and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or	• ALI 75/150 mg Q2W • EZE	Atorvastatin 20 or 40 mg ± other LLT (except EZE as it was used as a comparator)

	• N=355	LDL-C ≥100 mg/dL (for patients with no documented ASCVD) Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded		
8	OPTIONS II[12, 13] • 24 weeks • N=305	Patients with HeFH or non-FH, and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or LDL-C ≥100 mg/dL (for patients with no documented ASCVD) Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded	• ALI 75/150 mg Q2W • EZE	Rosuvastatin 10 or 20 mg ± other LLT (except EZE as it was used as a comparator)
9	ALTERNATIVE[14, 15] • 24 weeks	Statin-intolerant patients with HeFH or non-FH and moderate to very high CV risk,† with LDL-C ≥70 mg/dL (for	• ALI 75/150 mg Q2W • EZE	No statin, but other LLTs (except EZE) were allowed

	• N=361	patients with very high risk) or LDL-C ≥100 mg/dL (for patients with moderate or high risk) Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded		
10	MONO[16] • 24 weeks • N=103	Subjects with 10-year risk of fatal CV events of ≥1% and <5% based on SCORE, and LDL-C ≥70 and <190 mg/dL Patients with history of CHD, HeFH, DM associated with a risk SCORE ≥5% or any additional risk factor, or newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >8.5% at screening) were excluded	• ALI 75/150 mg Q2W • EZE	No statin or other LLT

11	CHOICE I[17] • 48 weeks • N=803	Patients with hypercholesterolemia at moderate to very high CV risk Patients with newly diagnosed DM (within 3 months prior to the screening visit) or poorly controlled DM (HbA1c >9% at the screening visit) were excluded	• ALI 300 mg Q4W/150 mg Q2W • ALI 75/150 mg Q2W • PBO	Maximally tolerated statin or no statin, both ± other LLT
12	CHOICE II[18] • 24 weeks • N=233	Patients with hypercholesterolemia at moderate to very high CV risk, and LDL-C ≥100 and <160 mg/dL for patients on diet therapy alone Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded	• ALI 150 mg Q4W/150 mg Q2W • ALI 75/150 mg Q2W • PBO	No statin, but receiving fenofibrate or EZE, or diet alone
13	OUTCOMES[19] • Median follow-up 2.8 years	Patients with recent acute coronary syndrome (within 1 year) and inadequate control of atherogenic lipoproteins (defined by at least one	• ALI 75/150 mg Q2W • PBO	Atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg daily, or the maximum tolerated or advisable dose

	• N=18,924	of the following: LDL-C ≥70 mg/dL, non-HDL-C≥ 100 mg/dL, or Apo B ≥80 mg/dL) on specified statin therapy No specified DM exclusion criteria		of one of these statins
14	DM-INSULIN[20, 21] • 24 weeks • N=517	Patients at high CV risk with T2DM or T1DM and LDL-C ≥70 mg/dL	• ALI 75/150 mg Q2W • PBO	Maximally tolerated statin or no statin, both ± other LLT
15	DM-DYSLIPIDEMIA[22, 23] • 24 weeks • N=413	Patients with T2DM and mixed dyslipidemia (defined as non-HDL-C ≥100 mg/dL, and triglycerides ≥150 and <500 mg/dL) with documented ASCVD or ≥1 additional CV risk factor	• ALI 75/150 mg Q2W • Usual care (EZE, fenofibrate, omega-3 fatty acids or nicotinic acid)	Maximally tolerated statin or no statin, without other LLT

EVOLOCUMAB Phase 3 PROFICIO trials				
1	DESCARTES[24] • 52 weeks • N=901	Patients with LDL-C ≥75 mg/dL (1.9 mmol/L) Excluded: • LDL-C ≤99 mg/dL (2.6 mmol/L) with CHD or CHD risk equivalent and not receiving a statin • T1DM or newly diagnosed T2DM (within 6 months of randomization or new screening FPG ≥126 mg/dL [7.0 mmol/L] or HbA1c ≥6.5%), or poorly controlled T2DM (HbA1c >8.5%)	Background LLT stabilized, then patients were randomized to receive EVO 420 mg Q4W OR PBO SC Q4W; 8 treatment groups: • Diet alone + EVO 420 mg Q4W • Diet alone + PBO SC Q4W • Diet + atorvastatin 10 mg QD + EVO 420 mg Q4W • Diet + atorvastatin 10 mg QD + PBO SC Q4W • Diet + atorvastatin 80 mg QD + EVO 420 mg Q4W • Diet + atorvastatin 80 mg QD + PBO SC Q4W • Diet + atorvastatin 80 mg QD + EZE 10 mg QD + EVO 420 mg Q4W • Diet + atorvastatin 80 mg QD + EZE 10 mg QD + PBO SC Q4W	LLT, ranging from diet alone to atorvastatin 80 mg plus EZE, was optimized to reach NCEP ATP III LDL-C treatment goals
2	MENDEL-2[25] • 12 weeks • N=614	Patients with LDL-C ≥100 and <190 mg/dL (≥2.6 and <4.9 mmol/L) Patients with DM were excluded	Six treatment groups: • EVO 140 mg Q2W + PBO PO QD • PBO SC Q2W + EZE PO QD • PBO SC Q2W + PBO PO QD • EVO 420 mg QM + PBO PO QD • PBO SC QM + EZE PO QD • PBO SC QM + PBO PO QD	None

3	LAPLACE-2[26, 27] • 12 weeks • N=1896	Patients with LDL-C ≥150 mg/dL (4.0 mmol/L) on no statin, ≥100 mg/dL (2.6 mmol/L) on nonintensive statin, or ≥80 mg/dL (2.1 mmol/L) on intensive statin Patients with T1DM or newly diagnosed or poorly controlled T2DM (HbA1c >8.5%) were excluded	24 treatment groups: Background atorvastatin 80 mg QD OR atorvastatin 10 mg QD, PLUS one of the following: • EVO 140 mg Q2W + PBO PO QD • PBO SC Q2W + EZE PO QD • PBO SC Q2W + PBO PO QD • EVO 420 mg QM + PBO PO QD • PBO SC QM + EZE PO QD • PBO SC QM + PBO PO QD OR Background rosuvastatin 40 mg QD OR rosuvastatin 5 mg QD OR simvastatin 40 mg QD, PLUS one of the following: • EVO 140 mg Q2W • PBO SC Q2W • EVO 420 mg QM • PBO SC QM	Five background statin regimens: atorvastatin 80 mg, atorvastatin 10 mg, rosuvastatin 40 mg, rosuvastatin 5 mg, or simvastatin 40 mg
4	GAUSS-2[28, 29]	Statin-intolerant patients not at LDL-C goal per NCEP ATP III risk	Four treatment groups: • EVO 140 mg Q2W + PBO PO QD	None, or on a low-dose statin defined as a

	• 12 weeks • N=307	categories for fasting LDL-C Patients with T1DM or newly diagnosed T2DM (within 6 months of randomization or new screening FPG ≥126 mg/dL [7.0 mmol/L] or HbA1c ≥6.5%), or poorly controlled T2DM (HbA1c >8.5%) were excluded	• EVO 420 mg QM + PBO PO QD • PBO SC Q2W + EZE PO QD • PBO SC QM + EZE PO QD	maximum weekly dose of ≤70 mg atorvastatin, ≤140 mg simvastatin/pravastatin/lovastatin, ≤35 mg rosuvastatin, or ≤280 mg fluvastatin
5	GAUSS-3[30] • 24 weeks (Phase A) + 2 weeks (washout) + 24 weeks (Phase B) • N=491 (Phase A), N=218 (Phase B)	Statin-intolerant patients with muscle-related adverse effects, not at LDL-C goal per NCEP ATP III risk categories for fasting LDL-C Patients with T1DM or newly diagnosed T2DM (within 6 months of randomization or new screening FPG ≥126 mg/dL [7.0 mmol/L] or HbA1c ≥6.5%), or poorly controlled T2DM (HbA1c >8.5%) were excluded	Phase A (24 weeks): atorvastatin 20 mg QD or PBO to identify patients having muscle-related symptoms only with atorvastatin but not PBO. These patients entered Phase B (24 weeks after a 2-week washout), and were randomized to EVO 420 mg QM or EZE 10 mg QD	Atorvastatin 20 mg QD
6	RUTHERFORD-2[31] • 12 weeks	Patients with HeFH and LDL-C ≥100 mg/dL (2.6 mmol/L)	Four treatment groups: • EVO 140 mg Q2W • PBO Q2W	On stable background statin with or without other approved LLT for ≥4 weeks

	• N=329	Patients with T1DM or newly diagnosed or poorly controlled T2DM (HbA1c >8.5%) were excluded	• EVO 420 mg QM • PBO QM	
7	THOMAS-1[32] • 6 weeks • N=149	Patients with LDL-C ≥85 mg/dL (2.2 mmol/L) Patients with T1DM, or uncontrolled or recently diagnosed T2DM, were excluded	EVO 140 mg SC Q2W with autoinjector versus prefilled syringe	On stable statin (with or without EZE) for ≥4 weeks before LDL-C screening
8	THOMAS-2[32] • 12 weeks • N=164	Patients with LDL-C ≥85 mg/dL (2.2 mmol/L) Patients with T1DM, or uncontrolled or recently diagnosed T2DM, were excluded	EVO 420 mg SC QM with autoinjector versus automated minidoser	On stable statin (with or without EZE) for ≥4 weeks before LDL-C screening
9	GLAGOV[33, 34] • 76 weeks • N=968	Patients with angiographic coronary disease, and LDL-C ≥80 mg/dL or 60−80 mg/dL with 1 major or 3 minor CV risk factors Patients with T1DM or poorly controlled T2DM (HbA1c >9%) at	• EVO 420 mg QM • PBO QM	On stable statin for ≥4 weeks before LDL-C screening

		screening were excluded		
10	FOURIER[35] • Median follow-up 2.2 years • N=27,564	Patients with ASCVD and LDL-C ≥70 mg/dL No specified DM exclusion criteria	Four treatment groups: • EVO 140 mg Q2W • PBO Q2W • EVO 420 mg QM • PBO QM	Optimized regimen of LLT, defined as preferably a high-intensity statin but must have been at least atorvastatin 20 mg daily or its equivalent, with or without EZE
11	NCT02739984 • 12 weeks • N=424	Patients with T2DM on stable DM therapy, LDL-C or non-HDL-C levels and fasting triglycerides ≤600 mg/dL, with HbA1c <10%	• EVO 420 mg QM • PBO QM	Maximally tolerated dose of statin of at least moderate intensity
12	NCT02662569 • 12 weeks • N=986	Patients with T2DM on stable DM therapy, and fasting LDL-C ≥100 mg/dL for those on statin or ≥130 mg/dL for those not on statin Patients with T1DM or poorly controlled T2DM were excluded	Four treatment groups: • EVO 140 mg Q2W • PBO Q2W • EVO 420 mg QM • PBO QM	Atorvastatin 20 mg PO QD

Clinicaltrials.gov identifiers: FH I, NCT01623115; FH II, NCT01709500; HIGH FH, NCT01617655; COMBO I, NCT01644175; COMBO II,

NCT01644188; LONG TERM, NCT01507831; OPTIONS I, NCT01730040; OPTIONS II, NCT01730053; ALTERNATIVE, NCT01709513; MONO, NCT01644474; CHOICE I, NCT01926782; CHOICE II, NCT02023879; OUTCOMES, NCT01663402; DM-INSULIN, NCT02585778; DM-DYSLIPIDEMIA, NCT02642159; DESCARTES, NCT01516879; MENDEL-2, NCT01763827; LAPLACE-2, NCT01763866; GAUSS-2, NCT01763905; GAUSS-3, NCT01984424; RUTHERFORD-2, NCT01763918; THOMAS-1, NCT01849497; THOMAS-2, NCT01879319; GLAGOV, NCT01813422; FOURIER, NCT01764633.

*Maximally tolerated statin dose = the highest tolerable registered dose of daily statin currently administered to the patient, i.e. rosuvastatin 20 or 40 mg, atorvastatin 40 or 80 mg, or simvastatin 80 mg. Lower doses could be used, e.g. in the case of intolerance or local practice, according to the investigator's judgment.

†Moderate risk = 10-year risk of fatal CV events of ≥1% and <5% (SCORE). High risk = SCORE ≥5%, eGFR 30 to <60 mL/min/1.73 m^2, T1DM or T2DM without target organ damage or HeFH. Very high risk = CHD, ischemic stroke, peripheral artery disease, transient ischemic attack, abdominal aortic aneurysm, or carotid artery occlusion >50% without symptoms; carotid endarterectomy or carotid artery stent procedure; renal artery stenosis or renal artery stent procedure; or T1DM or T2DM with target organ damage.

NCEP ATP III risk category LDL-C goals:[36] <100 mg/dL (2.6 mmol/L) for those with diagnosed CHD or risk equivalent, <130 mg/dL (3.4 mmol/L) for those without CHD or risk equivalent and ≥2 risk factors, <160 mg/dL (4.1 mmol/L) for those without CHD or risk equivalent and 1 risk factor, or <190 mg/dL (4.9 mmol/L) for those without CHD or risk equivalent and no risk factors.

ALI, alirocumab; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EVO, evolocumab; EZE, ezetimibe; FH, familial hypercholesterolemia; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; NCEP ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; PBO, placebo; PO, oral; Q2W, every two weeks; Q4W, every 4 weeks; QD, once daily; QM, monthly; SC, subcutaneous; SCORE, European Systematic Coronary Risk Evaluation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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