Oral PCSK9 Inhibition Arrives: Enlicitide (LIPFENDRA®) — FDA Approved July 2026

Clinical summary for UK & US prescribers · Dr Lucy Hooper MB BS MRCGP MA BSc DRCOG DCH · July 2026

~57%	~50%	~28%	20mg
LDL-C reduction	ApoB reduction	Lp(a) reduction	Once-daily oral dose
vs placebo at week 24	CORALreef Lipids	median, vs placebo	on empty stomach

MECHANISM OF ACTION

Enlicitide is a **novel macrocyclic peptide** — a ring-shaped small molecule designed to achieve biologic-like target specificity in an orally administered form. For years, oral delivery of peptide drugs has been a major pharmaceutical challenge; enlicitide represents a meaningful advance. It binds directly to PCSK9 and prevents PCSK9 from interacting with LDL receptors on hepatocyte surfaces.

By blocking PCSK9-mediated LDL receptor degradation, enlicitide increases the number of receptors available for LDL-C clearance — the same mechanism as evolocumab and alirocumab, but administered as a once-daily tablet.

MOLECULE CLASS

Class	Macrocyclic peptide PCSK9 inhibitor
Route	Oral once daily
Dose	20 mg
Administration	Empty stomach; wait ≥30 min before food or other oral medications
FDA indication	Adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolaemia, including HeFH (US, approved 17 Jul 2026)
Approval basis	LDL-C reduction (surrogate endpoint). CV event reduction not yet established.
Comparators	US: injectable PCSK9i (evolocumab, alirocumab), inclisiran, ezetimibe, bempedoic acid — access/formulary key issue UK: evolocumab, alirocumab (SC), inclisiran (SC 6-monthly via clinician)

REGULATORY & ACCESS STATUS

US (FDA): Approved 17 July 2026 (LIPFENDRA®). Immediate clinical questions: insurance coverage, prior authorisation, and formulary positioning versus injectable PCSK9 inhibitors, inclisiran, ezetimibe and bempedoic acid.

EU (EMA): MSD submitted a marketing authorisation application spring 2026. Approval realistically late 2027 at earliest.

UK (MHRA): No separate submission confirmed. Post-Brexit independent review — UK approval likely to follow EU decision.

INCLISIRAN COMPARISON

UK prescribers will most commonly compare enlicitide to **inclisiran** (Leqvio) — the most widely used PCSK9-directed therapy in NHS pathways, administered as a subcutaneous injection 6-monthly by a clinician. Enlicitide offers comparable LDL-C reduction (~57% vs ~50%) as a self-administered daily tablet — removing injection aversion, but reintroducing daily adherence as a determinant of efficacy. Injectables have near-perfect persistence once administered; daily tablets do not.

PIVOTAL TRIAL DATA

	CORALreef Lipids	CORALreef HeFH
N (enlicitide)	1,935	202
Population	ASCVD or high-risk primary prevention	Heterozygous FH
Background Rx	Statin ± ezetimibe (statin intolerance excluded)	Statin ± ezetimibe
Primary EP	Mean % ΔLDL-C baseline→wk 24	Mean % ΔLDL-C baseline→wk 24
LDL-C reduction (vs placebo)	–57% (ITT) –60% (post-hoc)	–59%
Non-HDL-C	–54%	–52%
ApoB	–50%	–48%
Lp(a) (median)	–28%	—
Guideline goal attainment	70% achieved <70 mg/dL + ≥50%↓	Not reported
Duration	52 weeks	52 weeks
Diarrhoea	Similar to placebo	7% vs 2%
Dizziness	Similar to placebo	9% vs 4%
Discontinuation	Similar to placebo	Similar to placebo

■ IMPORTANT LIMITATIONS

No cardiovascular outcomes data yet. CORALreef Outcomes (n>14,500) has estimated primary completion 2029. Approval based on surrogate lipid endpoints only. Injectable PCSK9 inhibitors (evolocumab, alirocumab) retain completed CV outcomes trial data.

CLINICAL BOTTOM LINE

Enlicitide (LIPFENDRA®) produces ~56% placebo-adjusted LDL-C reduction in ASCVD/high-risk patients and ~59% in HeFH — with 70% achieving guideline goals — in a once-daily oral formulation. FDA approval (17 Jul 2026) was based on LDL lowering as a surrogate endpoint: this does not yet establish reduction in MI or stroke. The Lp(a) reduction (~28%) is clinically significant for patients with known elevated Lp(a) awaiting an oral option. Evidence derives from patients on maximally tolerated statin therapy — extrapolation to statin-intolerant patients is premature. US prescribers: key issue is coverage and prior authorisation vs existing options. UK/EU prescribers: EMA submission in; MHRA submission not confirmed. CV outcomes data (CORALreef Outcomes, n>14,500) expected November 2029.

Sources: Navar AM et al. N Engl J Med 2026;394:529–539 (CORALreef Lipids, NCT05952856) · CORALreef HeFH (NCT05952869), JAMA 2025 · Merck press release 16 Jul 2026 · AJMC review 17 Jul 2026 · FDA Prescribing Information LIPFENDRA (enlicitide) 2026