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Review Article

Enlicitide (Lipfendra): the first oral PCSK9 inhibitor - from macrocyclic peptide innovation to clinical translation

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ABSTRACT

A substantial proportion of patients with hypercholesterolaemia, particularly those with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolaemia (HeFH), do not achieve recommended LDL-cholesterol (LDL-C) targets despite statins, ezetimibe, and injectable PCSK9 inhibitors. The parenteral route of the latter remains a well-recognised barrier to their wider use. Objective of the study was to review the discovery, pharmacology, clinical evidence, and therapeutic positioning of enlicitide (Lipfendra), the first oral PCSK9 inhibitor, approved by the US FDA in July 2026. A structured narrative review of PubMed/MEDLINE, ClinicalTrials.gov, FDA regulatory documents, and the primary CORALreef trial publications, with priority given to original clinical and discovery-chemistry sources over secondary reviews. Enlicitide is an orally bioavailable macrocyclic peptide that binds circulating PCSK9 and preserves hepatic LDL-receptor recycling. Across the CORALreef phase 3 programme, it produced placebo-adjusted LDL-C reductions of approximately 56–60%, with concordant reductions in apolipoprotein B, non-HDL-cholesterol, and lipoprotein(a). Its short-term safety profile was comparable to placebo. Its approval further demonstrates, for the first time, that a large extracellular protein-protein interaction, previously considered accessible only to injectable biologics, can be disrupted through an orally administered peptide. Enlicitide brings potent PCSK9 inhibition within an oral formulation for the first time. Whether this translates into reduced cardiovascular events, how it performs over long-term use, and how accessible it will prove outside the United States - including in India, where familial hypercholesterolaemia remains substantially underdiagnosed - are questions that current evidence cannot yet answer.

Keywords: Enlicitide, Lipfendra, PCSK9 inhibitor, Oral peptide, Macrocyclic peptide, Hypercholesterolaemia, LDL cholesterol, Cardiovascular pharmacology

INTRODUCTION

Atherosclerotic cardiovascular disease remains the foremost cause of mortality worldwide, and among its modifiable risk factors, elevated LDL-C stands out as the principal causal driver of atherogenesis. Epidemiological cohorts, Mendelian randomization analyses, and randomized trials converge on the same conclusion: cumulative lifetime exposure to LDL-C, rather than its level at any single point, determines cardiovascular risk.[1] Sustained LDL-C lowering, initiated as early as feasible, therefore remains the cornerstone of both primary and secondary prevention.

Statins continue to anchor this strategy, given their proven efficacy, favourable safety record, established outcome benefit, and affordability. Even so, a considerable proportion of high-risk patients fail to reach guideline-

recommended targets - some because of severe baseline hypercholesterolaemia or genetic dyslipidaemia, others because of statin intolerance, inadequate dose intensification, or suboptimal adherence. Ezetimibe, bempedoic acid, monoclonal PCSK9 antibodies, and small-interfering RNA (siRNA) therapy have progressively narrowed this treatment gap, yet it has not been closed.[2,3]

The discovery of PCSK9 ranks among the more consequential advances in lipid biology of the past two decades. Gain-of-function mutations in PCSK9 produce severe hypercholesterolaemia through accelerated LDL-receptor degradation, whereas loss-of-function variants confer lifelong LDL-C reduction and markedly attenuated cardiovascular risk - genetic validation as compelling as any cardiovascular drug target possesses.[1] This evidence underpinned the development of monoclonal antibodies and siRNA-based agents that preserve LDL-receptor recycling and have since demonstrated cardiovascular benefit in large outcome trials. All these agents, however, require parenteral administration, and this route has repeatedly been implicated in real-world underutilization relative to their trial-demonstrated efficacy.[3,4]

Because PCSK9 engages the LDL receptor across a broad extracellular interface, and because peptide therapeutics are typically degraded before oral absorption can occur, an orally active PCSK9 inhibitor was long regarded as one of the more formidable challenges in cardiovascular drug discovery.[4,5] The approval of enlicitide (Lipfendra) on 16 July 2026, as the first orally administered macrocyclic peptide PCSK9 inhibitor, represents the successful resolution of this challenge, and establishes a broader principle of considerable pharmacological interest: that biologic-like target engagement can now be achieved through an orally active peptide.[6,7]

This review examines enlicitide's discovery chemistry, mechanism of action, pharmacokinetics, clinical trial evidence, safety profile, and place in therapy, situating these within the context of other oral PCSK9-pathway agents now in development, before turning to a discussion of its relevance to India, where familial hypercholesterolaemia continues to go substantially underdiagnosed.

METHODS

This review was undertaken as a structured narrative review rather than a formal systematic review, an approach we consider appropriate given the recency of the agent and the multidisciplinary nature of the available evidence, spanning medicinal chemistry, regulatory science, and clinical trials. The literature searches encompassed PubMed/MEDLINE, ClinicalTrials.gov, FDA regulatory documents, and the reference lists of relevant publications, using combinations of the terms enlicitide, Lipfendra, MK-0616, oral PCSK9 inhibitor, macrocyclic peptide, hypercholesterolaemia, and the individual CORALreef trial names. Priority was accorded to original discovery papers, phase 2 and 3 clinical trials, and FDA prescribing information; review articles and meta-analyses were used to provide context and critical interpretation rather than as a substitute for primary evidence. Established findings are distinguished throughout from projections, computational models, and expert opinion.

PCSK9: FROM GENETIC DISCOVERY TO THERAPEUTIC TARGET

PCSK9 is synthesised predominantly by hepatocytes and secreted into the circulation, where it binds the epidermal growth factor-like repeat A (EGF-A) domain of the LDL receptor. This interaction diverts the receptor-PCSK9 complex toward lysosomal degradation during receptor-mediated endocytosis, rather than permitting the receptor to recycle to the cell surface. Fewer surface receptors translate into reduced hepatic clearance of circulating LDL-C, and consequently elevated plasma levels.[1,8] Pharmacological inhibition of PCSK9, by any mechanism, preserves this recycling and thereby augments hepatic LDL clearance. A further point of mechanistic interest is that statins increase hepatic expression of both the LDL receptor and PCSK9 through SREBP-2-mediated upregulation; inhibiting PCSK9 therefore protects the very receptors that statin therapy induces, which provides a coherent pharmacological rationale for combining the two classes rather than viewing them as competing strategies.[1,8]

THE EVOLUTION OF PCSK9-DIRECTED THERAPY

The evolution of PCSK9-directed therapy is shown in Figure 1.

The earliest PCSK9-directed agents were injectable monoclonal antibodies - evolocumab and alirocumab - which bind circulating PCSK9 with high affinity and have since demonstrated cardiovascular outcome benefit in large randomized trials. Inclisiran, an siRNA-based therapy, subsequently permitted a substantially longer dosing interval by suppressing hepatic PCSK9 synthesis at the transcriptional level rather than neutralizing the circulating protein. Despite the considerable efficacy of these agents, subcutaneous administration, cold-chain requirements, reimbursement hurdles, and patient reluctance to initiate long-term injectable therapy have collectively constrained their real-world uptake well below what trial efficacy alone would predict.[2-4]

Enlicitide is one of several oral agents currently under development in this therapeutic area, and placing it in the context of emerging competitors helps illustrate the rapidly evolving treatment landscape.[9] NNC0385-0434 (Novo Nordisk), an alternative oral peptide-based inhibitor, showed comparable efficacy in a phase 2 trial reported in 2024.[10] Lerodalcibep, a small recombinant PCSK9-binding protein administered by monthly injection

rather than orally, is frequently discussed alongside these oral candidates given its shared mechanistic target, though it remains a parenteral agent in the strict sense.[3] These agents are chemically and developmentally distinct from enlicitide, and in the absence of head-to-head trials, any comparison across them warrants due caution.

DISCOVERY AND MOLECULAR ENGINEERING OF ENLICITIDE

Enlicitide (development code MK-0616) was purpose-engineered to disrupt the extensive PCSK9-LDLR interface that conventional drug-like small molecules are poorly suited to address.[5,11] The discovery programme employed mRNA-display screening - a technique capable of interrogating vast macrocyclic peptide libraries simultaneously - to identify candidates binding PCSK9 with high affinity, followed by iterative, issue-driven fragment-based synthetic assembly to optimize binding affinity, conformational stability, proteolytic resistance, and, critically, oral bioavailability.[5,11,12] Macrocyclization constrains the peptide into a favoured three-dimensional conformation, conferring both the target affinity and the proteolytic resilience that a linear peptide of comparable size could not achieve - properties indispensable to successful oral administration.[5]

Discovery of a molecule with this degree of structural complexity necessarily required parallel innovation in manufacturing chemistry. A convergent biocatalytic route, employing enzyme cascades in place of numerous discrete chemical transformations, substantially shortened the synthetic sequence relative to earlier approaches, while dedicated total-synthesis and process-development work addressed fragment assembly, purification, and scale-up.[13-16] Taken together, this body of work establishes enlicitide as the first clinically approved oral PCSK9 inhibitor and, more broadly, as proof-of-concept that engineered macrocyclic peptides can now reach extracellular protein-protein interaction targets previously considered the exclusive domain of injectable biologics.

MECHANISM OF ACTION

Enlicitide acts entirely within the extracellular compartment, binding circulating PCSK9 before it can engage the LDL receptor - a mechanism distinct from that of statins, which act intracellularly by curtailing cholesterol biosynthesis. By preventing the PCSK9-LDLR interaction, enlicitide preserves physiological receptor recycling, thereby increasing hepatocyte-surface receptor density, hepatic LDL clearance, and, consequently, lowering plasma LDL-C.[6,8] This mechanism (Figure 2) is mechanistically complementary to statin therapy: statins upregulate LDL-receptor expression, while enlicitide protects the additional receptors thus generated from PCSK9-mediated degradation - a rationale that favours combination use over substitution.[1,8]

PHARMACODYNAMICS

Beyond LDL-C lowering, enlicitide reduces apolipoprotein B - reflecting a lower burden of circulating atherogenic particles - together with non-HDL-cholesterol. It also reduces lipoprotein(a), albeit more modestly and through a mechanism not yet fully characterised, a pattern consistent with the class effect reported across other PCSK9-directed therapies.[17,18] Available trial data indicate that the LDL-C-lowering effect is sustained through the treatment period without evidence of attenuation over time; confirmation of its durability beyond current follow-up will require extension studies and post-marketing surveillance.[6,7]

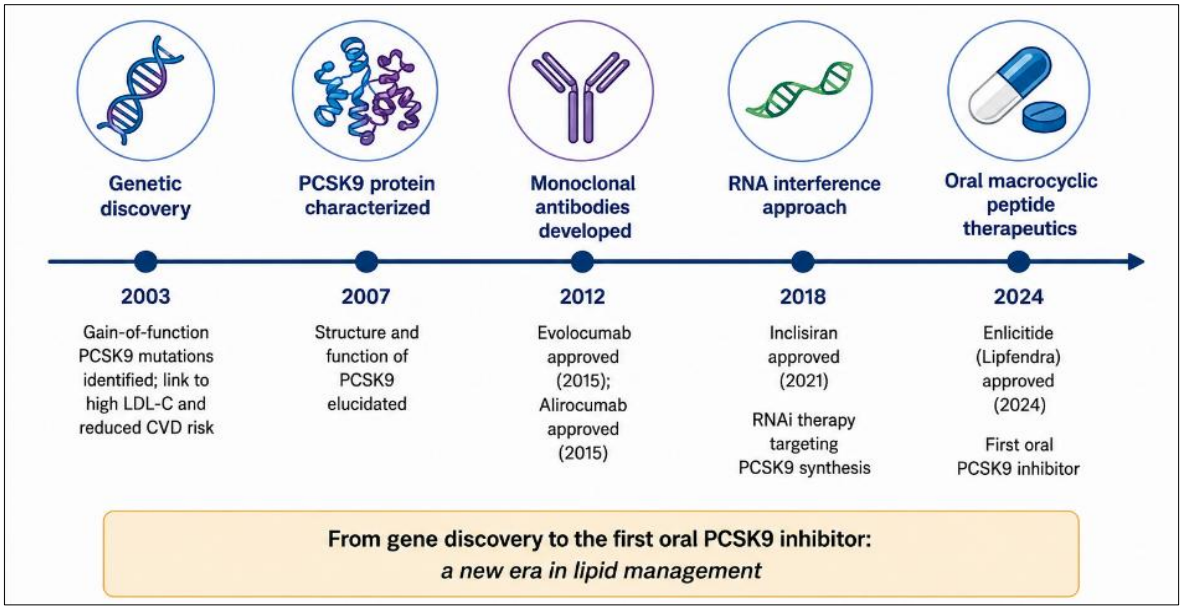

Figure 1: Evolution of PCSK9-directed therapy.

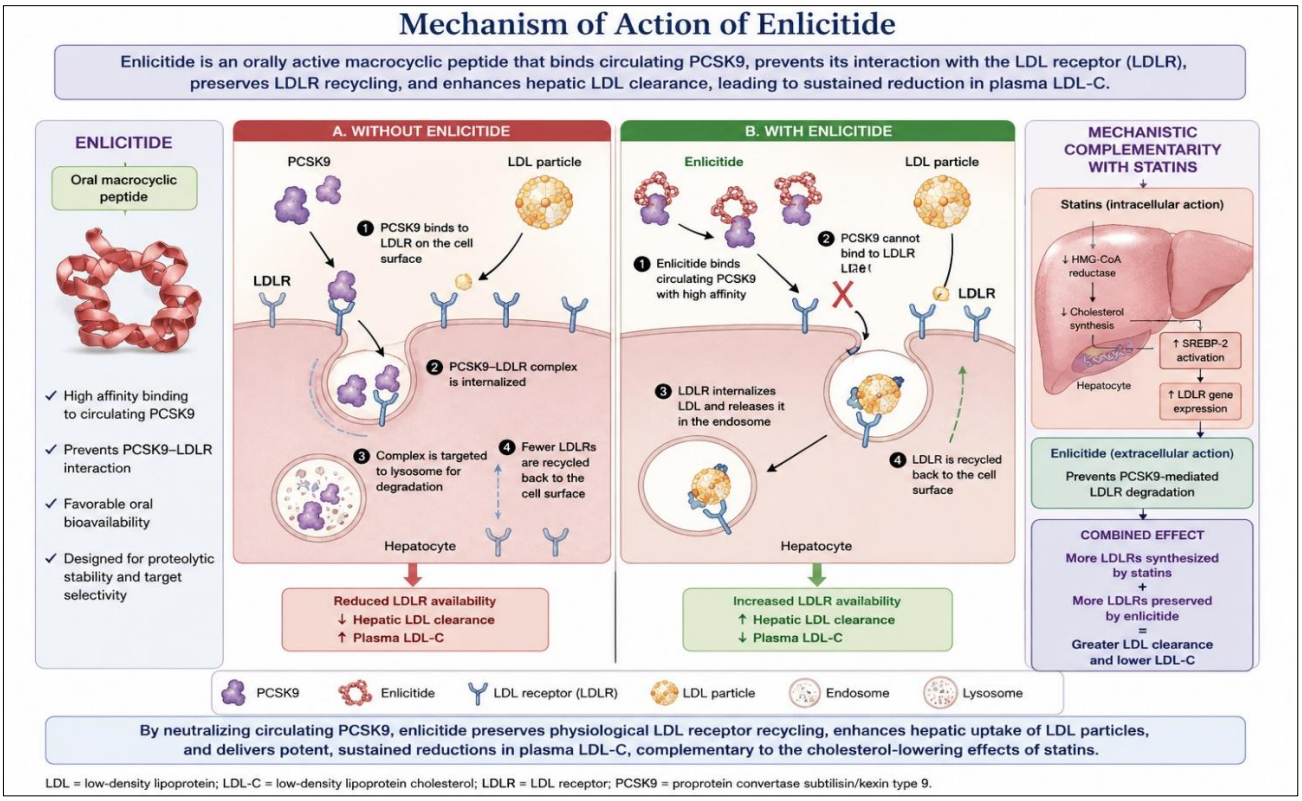

Figure 2: Mechanism of action of enlicitide.

CLINICAL PHARMACOKINETICS

Enlicitide is administered as a 20 mg oral tablet once daily. The salient pharmacokinetic characteristics, derived from the approved US prescribing information, are summarized below.[19]

Absorption

Administered in the morning on an empty stomach, at least 30 minutes before food, with water, black coffee, or plain tea only; dosing 30 minutes after a meal reduces steady-state AUC and Cmax by approximately 48% and 50% respectively.

Protein binding

Concentration-dependent, ranging from approximately 32% to 93%.

Elimination half-life

Approximately 14 hours; clearance increases with increasing concentration, giving rise to non-linear pharmacokinetics.

Metabolism

Predominantly proteolytic rather than cytochrome P450-mediated; no major circulating metabolites have been identified.

Excretion

Primarily via glomerular filtration, with a smaller faecal component.

Special populations

No clinically meaningful effect of age (18–88 years), body weight, sex, or ethnicity has been observed.

Moderate and severe renal impairment are associated with modestly higher steady-state exposure, without a specific dose-adjustment recommendation at present.

Drug interactions

A dedicated phase 1 study found no clinically meaningful effect of enlicitide on the pharmacokinetics of co-administered narrow therapeutic index medications, consistent with its minimal reliance on CYP-mediated metabolism.[19,20]

Because enlicitide's target is extracellular, tissue accumulation is not a prerequisite for efficacy. The principal practical consideration in clinical use is therefore administration timing - reconciling the fasting-dose requirement with a patient's other morning medications - rather than a conventional pharmacokinetic drug-drug interaction.[19,20]

CLINICAL DEVELOPMENT PROGRAMME: THE CORALREEF TRIALS

The enlicitide development programme progressed from early pharmacokinetic and safety studies, through phase 2b dose optimization, to a large multinational phase 3 programme designated CORALreef, evaluating oral bioavailability, dose selection, tolerability, and integration with existing lipid-lowering therapy at each successive stage.

Phase 1 established that oral administration achieves systemic exposure sufficient to inhibit circulating PCSK9 and produce measurable LDL-C reduction, informed the fasting-administration recommendation, and confirmed the absence of a clinically meaningful interaction with narrow therapeutic index concomitant medications.[20]

Phase 2b (MK-0616) demonstrated a clear dose-dependent LDL-C reduction, with the highest doses approaching reductions historically reported for the injectable monoclonal antibodies, alongside improvements in apolipoprotein B and non-HDL-cholesterol and a placebo-comparable safety profile. This trial identified the dose subsequently carried forward into phase 3.[21]

CORALreef lipids (NCT05952856), the principal registration trial, was a multinational, double-blind, randomised, placebo-controlled study in 2,909 adults with hypercholesterolaemia, with and without HeFH, at established or high risk of a first ASCVD event, maintained on background statin therapy. At week 24, enlicitide produced a placebo-adjusted LDL-C reduction of approximately 56% (up to ~60% in a post-hoc reanalysis), with significant reductions in non-HDL-cholesterol, apolipoprotein B, and lipoprotein (a), sustained through week 52; the frequency of adverse reactions was comparable to placebo.[6,17]

CORALreef HeFH (NCT05952869) evaluated enlicitide specifically in heterozygous familial hypercholesterolaemia maintained on stable background therapy, demonstrating a placebo-adjusted LDL-C reduction of approximately 59% at week 24, with a safety profile broadly consistent with CORALreef Lipids. This finding is of particular clinical significance, as HeFH patients are traditionally among the most difficult to bring to target with existing therapy.[7,17]

Enlicitide versus oral non-statin therapies was a further phase 3 trial that reinforced enlicitide's role as an adjunct to, rather than a replacement for, statins and other oral agents.[22]

Pooled and subgroup analyses, including a combined analysis across CORALreef Lipids and CORALreef HeFH and a further analysis stratified by diabetes status, have been broadly consistent with the pivotal trial findings, without indicating a meaningfully different efficacy or tolerability profile according to diabetes status.[17,23] A published correspondence following the primary NEJM report raised methodological questions regarding trial interpretation - a normal feature of post-publication scientific scrutiny for any pivotal cardiometabolic trial.[24]

Cardiovascular outcomes remain to be established. Reduction of a surrogate lipid marker, however substantial, does not by itself establish a reduction in cardiovascular events. The dedicated outcomes trial, CORALreef outcomes (NCT06008756), has completed enrolment of approximately 14,500 participants and is projected to report only around 2029. Until then, the evidentiary basis for enlicitide's use rests on its demonstrated LDL-C-lowering effect, interpreted in light of the well-established epidemiological relationship between cumulative LDL-C reduction and cardiovascular risk observed with earlier agents.[6,25] Simulation-model analyses projecting comparative cardiovascular outcomes against ezetimibe, and mechanistic computational models predicting lipid-lowering efficacy, have also been published; these remain modelled projections rather than observed outcomes and should be interpreted accordingly.[26,27]

STRENGTHS AND LIMITATIONS OF THE CURRENT EVIDENCE BASE

The programme's principal strengths lie in its logical translational sequence from early pharmacokinetics through large multinational efficacy trials, its evaluation across clinically distinct populations, its assessment of lipid parameters beyond LDL-C alone, and the consistency of its safety signal at each successive stage. Its principal limitations are equally clear: the evidence rests on surrogate endpoints rather than demonstrated cardiovascular benefit, follow-up remains short relative to the anticipated duration of therapy, real-world adherence and effectiveness data are as yet unavailable, and the cost-effectiveness of enlicitide across differing healthcare systems, India's among them, has not been established.

SAFETY, TOLERABILITY, AND ADVERSE EFFECTS

Across the clinical programme, the overall incidence of treatment-emergent adverse events with enlicitide was comparable to placebo, with most reported events of mild to moderate severity.[6,7,19] In CORALreef HeFH specifically, dizziness (9% versus 4% with placebo) and diarrhoea (7% versus 2%) occurred more frequently with enlicitide; discontinuation rates attributable to adverse events, however, were similar between arms in both pivotal trials.[7,19] The oral route confers the additional advantage of eliminating injection-site reactions, among the more frequently cited treatment-related events with the parenteral PCSK9 inhibitors, which may in turn favour patient acceptance among those otherwise reluctant to initiate injectable therapy.[3,19]

As a peptide therapeutic, immunogenicity warrants consideration, though the oral route plausibly carries lower immunogenic potential than repeated parenteral administration of a large biologic; this will require confirmation through longer-term surveillance. No consistent signal of hepatotoxicity, nephrotoxicity, or myotoxicity has emerged to date, distinguishing enlicitide from certain established lipid-lowering agents that necessitate periodic biochemical monitoring - though routine lipid assessment, and the usual liver and renal monitoring that good clinical practice would in any case entail, remain appropriate.[19] Mechanistically, the reduction of cholesterol and cholesterol-derived substances underlies a labelled caution regarding possible fetal harm in pregnancy; adequate data in pregnancy and lactation are not yet available, and current regulatory guidance should be followed in this regard.[19] As with any peptide or protein therapeutic, hypersensitivity reactions are a recognized, if uncommon, concern warranting prompt discontinuation and medical attention should they occur.

DRUG-DRUG INTERACTIONS AND SPECIAL POPULATIONS

Available pharmacokinetic evidence, including a dedicated phase 1 interaction study in patients receiving narrow therapeutic index concomitant medications, indicates limited clinically significant interaction potential through the cytochrome system, consistent with enlicitide's predominantly proteolytic metabolism.[19,20] In clinical practice, the principal consideration is therefore administration timing - accommodating the fasting-dose requirement alongside a patient's other morning medications - rather than a true pharmacokinetic interaction.

Older adults

Efficacy and tolerability appear preserved across the studied age range (18–88 years), though continued evaluation in frail elderly populations would be valuable.[19]

HeFH

It is directly supported by CORALreef HeFH.[7]

Renal impairment

No major safety signal identified to date; moderate-to-severe impairment is associated with modestly higher exposure; dedicated data in advanced renal disease remain limited.[19]

Hepatic impairment

Given the hepatic locus of its pharmacological action, further data would be of value; current prescribing recommendations should be followed pending this.

Pregnancy and lactation

Adequate data are not yet available; the mechanism-based caution regarding fetal harm applies, and current regulatory guidance should be followed.

Table 1: Comparative pharmacology.

Drug/class	Target	Route	Frequency	Principal mechanism	Cardiovascular outcome evidence
Statins	HMG-CoA reductase	Oral	Daily	↓ Cholesterol synthesis	Established
Ezetimibe	NPC1L1	Oral	Daily	↓ Cholesterol absorption	Established
Bempedoic acid	ATP citrate lyase	Oral	Daily	↓ Cholesterol synthesis	Established
Evolocumab	Circulating PCSK9	SC injection	Every 2–4 weeks	Preserves LDLR recycling	Established
Alirocumab	Circulating PCSK9	SC injection	Every 2 weeks	Preserves LDLR recycling	Established
Inclisiran	Hepatic PCSK9 mRNA	SC injection	Twice yearly	Reduces PCSK9 synthesis	Outcome studies ongoing
Lerodalcibep	Circulating PCSK9	SC injection	Monthly	Preserves LDLR recycling	Outcome studies ongoing
AZD0780 (investigational)	PCSK9 (small molecule)	Oral	Daily	Distinct oral small-molecule mechanism	Phase 2 only
NNC0385-0434 (investigational)	Circulating PCSK9	Oral	Daily	Oral peptide, preserves LDLR recycling	Phase 2 only
Enlicitide (Lipfendra)	Circulating PCSK9	Oral	Daily	Macrocyclic peptide; preserves LDLR recycling	Outcome studies ongoing (CORALreef outcomes, ~2029)

THERAPEUTIC POSITIONING

Enlicitide is properly regarded as an adjunct to, rather than a substitute for, existing lipid-lowering therapy. Its most plausible clinical utility lies among patients who remain above target despite statins with or without ezetimibe, those who decline injectable therapy on grounds of needle aversion or preference, those requiring additional LDL-C lowering before an injectable biologic is contemplated, and patients with HeFH requiring combination therapy. The injectable monoclonal antibodies retain the strongest cardiovascular outcome evidence of any agent in this class; pending comparable outcome data for enlicitide, therapeutic decisions should weigh the relative strength of existing evidence against patient preference, accessibility, cost, and anticipated adherence.[3,6]

THE INDIAN PERSPECTIVE: AN UNDER-APPRECIATED TRANSLATIONAL QUESTION

Much of the international discourse surrounding enlicitide's approval has, understandably, centred on the US injectable-PCSK9-inhibitor landscape it now enters. A distinct and arguably more pressing question for Indian clinicians and pharmacologists concerns what an oral PCSK9 inhibitor might mean for the identification and management of familial hypercholesterolaemia within India specifically.

FH is estimated to affect approximately 1 in 250–500 individuals worldwide, a prevalence that could plausibly translate to several million affected individuals in India, yet the condition remains markedly underdiagnosed. Available Indian data, though limited, are instructive: one North Indian cohort reported FH in as many as 15% of patients with premature coronary artery disease, and a more recent regional study from Jharkhand, applying Dutch Lipid Clinic Network criteria, identified probable FH in nearly a quarter of patients with confirmed premature CAD.[28,29] Genetic testing infrastructure for FH remains confined to a small number of Indian centres, and no unified national registry yet exists, though some centres have begun contributing to international collaborative efforts.[28]

Existing injectable PCSK9 inhibitors have accordingly seen limited uptake in Indian clinical practice, constrained by acquisition cost, cold-chain and administration logistics, and the continued under-recognition of FH as a distinct diagnostic entity rather than merely "severe hypercholesterolaemia." An oral agent, should it reach the Indian market at an accessible price, could in principle mitigate some of these barriers - obviating injection-technique training and home cold-chain management - while introducing its own adherence burden in the form of daily fasting-state dosing, and remaining, at least initially, unlikely to undercut generic statins on cost. Two considerations should temper undue enthusiasm on this point. First, enlicitide has not yet received approval from India's Central Drugs Standard Control Organisation (CDSCO), and Indian regulatory timelines for comparable biologic-adjacent agents have historically lagged behind US and European approval by a variable interval. Second, reported US pricing has no direct bearing on eventual Indian pricing, which will depend on patent status, any licensing arrangements, and India's own pharmaceutical pricing framework, none of which can be responsibly predicted at this juncture.

For undergraduate and postgraduate medical education, enlicitide's approval nonetheless furnishes a timely and concrete teaching opportunity. It illustrates, within a single contemporary example, the principle of macrocyclic peptide engineering overcoming a historically "undruggable" protein-protein interaction target, and offers a live case through which to teach the distinction between surrogate-marker approval and outcomes-trial evidence - a distinction that, in our experience, receives insufficient emphasis at the undergraduate level in Indian curricula, despite its centrality to the critical appraisal of any new drug.

REMAINING EVIDENCE GAPS AND FUTURE DIRECTIONS

The most immediate priority is confirmation that enlicitide's substantial LDL-C reduction translates into reduced cardiovascular morbidity and mortality, a question CORALreef Outcomes is specifically designed to answer.[25] Long-term safety, immunogenicity, and hepatic tolerability warrant continued pharmacovigilance beyond the relatively short follow-up available at present. Populations underrepresented in the pivotal trials - advanced chronic kidney disease, severe hepatic impairment, the very elderly, and those on complex polypharmacy regimens - require dedicated study, as does real-world treatment persistence given the fasting-dose requirement. Comparative pharmacoeconomic evaluation against monoclonal antibodies, inclisiran, lerodalcibep, and the emerging oral competitors (AZD0780, NNC0385-0434) will be central to determining reimbursement and guideline positioning across healthcare systems, India included.[3,9,10] More broadly, the success of enlicitide suggests that macrocyclic peptide engineering may extend to other extracellular protein-protein interaction targets across inflammatory disease, oncology, endocrinology, and nephrology, well beyond the domain of lipid management.[5,11]

Clinical pearls

Enlicitide is the first orally administered PCSK9 inhibitor, a substantial advance in peptide drug development achieved through engineered macrocyclic peptide chemistry.

Its mechanism complements statin therapy by preserving LDL-receptor recycling rather than reducing cholesterol synthesis.

Oral administration eliminates injection-site reactions but introduces a fasting-state dosing requirement that patients must be counselled on.

Current evidence strongly supports LDL-C, apolipoprotein B, and lipoprotein (a) lowering; dedicated cardiovascular outcome data are not anticipated before 2029.

It is one of several oral or next-generation PCSK9-pathway agents in development, alongside AZD0780, NNC0385-0434, and lerodalcibep - none interchangeable, and none yet outcome-proven.

Judicious patient selection, adherence counselling, and, in the Indian context specifically, a heightened index of suspicion for underdiagnosed FH, will be essential to realizing its therapeutic benefit.

CONCLUSION

Enlicitide (Lipfendra) represents a genuine advance in lipid-lowering pharmacotherapy: the first orally administered PCSK9 inhibitor, engineered through sophisticated macrocyclic peptide chemistry to disrupt an extracellular protein-protein interaction previously considered accessible only to injectable biologics. Across the CORALreef programme, it achieves LDL-C, apolipoprotein B, and lipoprotein (a) reductions comparable to established injectable PCSK9 inhibitors, with a reassuring short-term safety profile. Its ultimate clinical significance - whether this surrogate-marker efficacy translates into reduced cardiovascular events, whether real-world adherence to daily fasting-state dosing matches trial conditions, and whether it becomes accessible and affordable outside the United States, including in India, where familial hypercholesterolaemia remains substantially underdiagnosed - is yet to be determined, and will ultimately decide its place in both global and Indian lipid-management practice.

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REFERENCES

1. Liu C, Chen J, Chen H, Zhang T, He D, Luo Q, et al. PCSK9 inhibition: from current advances to evolving future. Cells. 2022;11:2972.
2. Agarwala A, Asim R, Ballantyne C. Oral PCSK9 inhibitors. Curr Atheroscler Rep. 2024;26:147-52.
3. Tokgözoğlu L, Pirillo A, Catapano A. Oral PCSK9 inhibitors: will they work? Curr Atheroscler Rep. 2025;27.
4. Ferri N, Marodin G. Emerging oral therapeutic strategies for inhibiting PCSK9. Atheroscler Plus. 2024;59:25-31.
5. Josien H, Nair AG, Ding F, Guo Y, Chen Y-H, Rao AU, et al. Discovery process of enlicitide, a highly engineered macrocyclic peptide therapeutic, through issue-driven fragment-based synthetic assembly and SAR. J Med Chem. 2026;69(11):13473-91.
6. Navar A, Mikhailova E, Catapano A, Banka P, Blom D, Cadena A, et al. A placebo-controlled trial of the oral PCSK9 inhibitor enlicitide. N Engl J Med. 2026; 394(6):529-39.
7. Ballantyne CM, Gellis LA, Tardif J, Banka P, Navar A, Asprusten E, et al. Efficacy and safety of oral PCSK9 inhibitor enlicitide in adults with heterozygous familial hypercholesterolemia: a randomized clinical trial. JAMA. 2026;335(2):129-39.
8. Amorosi A, Varret M. PCSK9 in vascular smooth muscle cells: biology, pathology, and inhibition to fight atherosclerosis. Atheroscler Plus. 2026;64:9-23.
9. Koren MJ, Vega RB, Agrawal N, Xu Y, Barbour AM, Yu H, et al. An oral PCSK9 inhibitor for treatment of hypercholesterolemia: the PURSUIT randomized trial [AZD0780]. J Am Coll Cardiol. 2025;85(21):1996-2007.
10. Koren MJ, Descamps O, Hata Y, Hengeveld EM, Hovingh GK, Ikonomidis I, et al. PCSK9 inhibition with orally administered NNC0385-0434 in hypercholesterolaemia: a randomised, double-blind, placebo-controlled and active-controlled phase 2 trial. Lancet Diabetes Endocrinol. 2024;12(3):174-83.
11. Johnston J. Invention of enlicitide: from mRNA display to phase II [abstract 6804]. J Biol Chem. 2026;302:111964.
12. Campeau L-C. From cortisone to enlicitide: a journey of synthetic chemistry innovations at Merck. J Org Chem. 2025;90:4781-95.
13. Klapars A, Fryszkowska A, Galanie S, Ad O, Aguilera EY, Akporji N, et al. Biocatalytic cascades enable manufacture of the macrocyclic peptide enlicitide. Science. 2026;392(6798):643-7.
14. Li H, Thaisrivongs D, Shang G, Chen Y, Chen Q, Tan L, et al. Total synthesis of enlicitide decanoate. J Am Chem Soc. 2025;147(13):11036-48.
15. Jung W-O, Moor SR, An C, Christensen M, Dalby SM, Fan Y, et al. Development of direct liquid–liquid extraction of an enzymatic cascade en route to enlicitide using an automated, high-throughput screening platform. Synthesis. 2025;58:997-1002.
16. Xiao K-J, Chen Y, Xu Y, Shang G, Tan L, Xie F, et al. Process development toward a key fragment of the PCSK9 inhibitor enlicitide decanoate. Org Process Res Dev. 2025;29(4):1083-92.
17. Ballantyne CM, Mikhailova E, Catapano A, Blom D, Asprusten E, Banka P, et al. Pooled efficacy and safety of enlicitide, an oral PCSK9 inhibitor, across two phase 3 trials: CORALreef Lipids and CORALreef HeFH. J Clin Lipidol. 2026;20(6):121-2.
18. Mulligan M, Gandhi R, Vishwakarma R, Bhattacharya R. Lipoprotein (a) reduction with inclisiran, alirocumab, evolocumab, enlicitide, and lerodalcibep: a systematic review and meta-analysis of randomized controlled trials. J Clin Lipidol. 2026;20(6):1054-64.
19. Sharp M, Dohme LLC. LIPFENDRA (enlicitide) tablets, for oral use: highlights of prescribing

information. Rahway (NJ): Merck Sharp & Dohme LLC; 2026.
20. Johns DG, Alicea J, Auger P, Bajwa EK, Banka P, Basak P, et al. Phase 1 update: the novel oral PCSK9 inhibitor enlicitide does not affect the pharmacokinetics of narrow therapeutic index concomitant medications. J Am Coll Cardiol. 2026;87:13.
21. Ballantyne CM, Banka P, Mendez G, Garcia R, Rosenstock J, Rodgers A, et al. Phase 2b randomized trial of the oral PCSK9 inhibitor MK-0616. J Am Coll Cardiol. 2023;81(16):1553-64.
22. Catapano A, Mikhailova E, Navar A, Banka P, Corral P, Saxena M, et al. Oral PCSK9 inhibitor enlicitide versus oral nonstatin therapies: a phase 3 randomized clinical trial. J Am Coll Cardiol. 2026;88(3):340-52.
23. Lepor N, Parham J, Catapano A, Cadena A, Baum SJ, Navar A, et al. Efficacy and safety of enlicitide, an oral PCSK9 inhibitor, in participants with and without diabetes mellitus in a pooled analysis of two phase 3 trials. Diabetes. 2026;75:1.
24. Fan H, Zhou B. Trial of the oral PCSK9 inhibitor enlicitide. N Engl J Med. 2026;394(18):1867.
25. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Outcomes study of MK-0616 in participants with atherosclerotic cardiovascular disease (CORALreef Outcomes). Available at: https://clinicaltrials.gov/study/NCT06008756. Accessed on 15 May 2026.
26. Desai NR, Galvain T, Meng Y, Patil D, Brand-Wiita S, Eutsler J, et al. Comparative cardiovascular outcomes of enlicitide versus ezetimibe in patients with hypercholesterolemia: a simulation model analysis. J Clin Lipidol. 2026;20(6):e78.
27. Cariou B, Wang Y, Angoulvant D, Boccara F, Mahé G, Steg P, et al. In silico prediction of the lipid-lowering efficacy of the oral PCSK9 inhibitor enlicitide using a mechanistic computational model. Atherosclerosis. 2026;415:120682.
28. Reddy LL, Shah SAV, Ashavaid TF. Shortcomings on genetic testing of familial hypercholesterolemia (FH) in India: can we collaborate to establish Indian FH registry? Indian Heart J. 2022;74(1):1-6.
29. Kumar P, Prasad SR, Anand A, Kumar R, Ghosh S. Prevalence of familial hypercholesterolemia in patients with confirmed premature coronary artery disease in Ranchi, Jharkhand. Egypt Heart J. 2022;74:91.
30. US Food and Drug Administration. FDA approves first oral PCSK9 inhibitor to lower LDL cholesterol in adults with high cholesterol [news release]. Silver Spring (MD): FDA; 2026.

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