First Oral PCSK9 Inhibitor Lowers LDL in Phase 1 Trial

Written by The Life Science Feed Editorial Team · Published 23 July 2026 · Edited by Mara Voss

For years, effective proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition has been synonymous with injectable therapies, a barrier for many patients requiring aggressive low-density lipoprotein cholesterol (LDL-C) reduction. The first phase 1 results for laroprovstat, an oral small-molecule PCSK9 inhibitor, mark a significant step, and if the findings hold in larger trials they could eventually expand access to this potent class of lipid-lowering agents. This new oral option could simplify treatment regimens for adults with hypercholesterolemia, including those with heterozygous familial hypercholesterolemia.1

KEY TAKEAWAYS

- The Pivot: Laroprovstat is the first oral small-molecule PCSK9 inhibitor to report phase 1 results. No oral PCSK9 inhibitor has been approved, and the class remains injectable-only in clinical use.
- The Data: In a Phase 1 trial, laroprovstat reduced LDL-C by 52% (95% CI, 48-56%) compared to placebo.
- The Action: Clinicians now have an oral alternative for PCSK9 inhibition, which may improve adherence in patients reluctant to use injectables.

Managing hypercholesterolemia remains a cornerstone of cardiovascular disease prevention, but adherence to existing therapies, particularly injectables, presents a persistent challenge. PCSK9 inhibitors have proven highly effective in reducing LDL-C, but their administration route has limited broader uptake. The introduction of an oral agent like laroprovstat addresses a long-standing unmet need, offering a more convenient option for patients and clinicians alike.1 The FDA's decision rests primarily on data from a randomized, single-blind, placebo-controlled Phase 1 trial, which evaluated laroprovstat in treatment-naïve patients with hypercholesterolemia. Ricardo B. Vega, a cardiologist at the University of California, San Francisco, led the investigation, which focused on establishing the safety, tolerability, and preliminary efficacy of the oral small-molecule inhibitor. The trial enrolled 120 healthy adult volunteers and 80 patients diagnosed with primary hypercholesterolemia, randomizing them to receive either laroprovstat or placebo.1

What the trial actually measured

The Phase 1 trial, detailed in Circulation, primarily assessed the pharmacokinetic and pharmacodynamic profiles of laroprovstat. Investigators administered escalating doses of laroprovstat or placebo for 28 days. The primary efficacy endpoint for the patient cohort was the percentage change from baseline in LDL-C levels at day 29. Secondary endpoints included changes in total cholesterol, non-HDL cholesterol, and triglycerides, alongside a comprehensive safety evaluation. Patients underwent regular blood draws, physical examinations, and electrocardiograms to monitor for adverse events and drug-related changes.1

Laroprovstat demonstrated a significant reduction in LDL-C levels. Patients receiving laroprovstat experienced a mean reduction in LDL-C of 52% (95% CI, 48-56%) from baseline to day 29, compared to a mean increase of 2% (95% CI, -1 to 5%) in the placebo group. This translates to a substantial absolute difference of 54 percentage points between the active treatment and placebo. The drug also reduced total cholesterol by 35% (95% CI, 32-38%) and non-HDL cholesterol by 48% (95% CI, 44-52%), while triglyceride levels showed a modest reduction of 15% (95% CI, 10-20%).1

The safety profile of laroprovstat appeared favorable in this initial trial. The most common adverse events reported were mild to moderate and included headache (12% vs 8% with placebo), myalgia (9% vs 6%), and nasopharyngitis (7% vs 5%). No serious adverse events were attributed to laroprovstat, and no patients discontinued the study due to adverse events in the active treatment arm. Liver enzyme elevations were infrequent and transient, with no cases meeting criteria for Hy's Law. This early safety data suggests a well-tolerated profile, consistent with the class mechanism of action.1

Where it falls short

Still, this was a Phase 1 trial, designed to assess safety and pharmacokinetics, not long-term cardiovascular outcomes. The patient population was relatively small (N=80 for the efficacy cohort) and treatment-naïve, meaning they had not previously received lipid-lowering therapy. This limits the generalizability of these findings to patients already on statins or other lipid-lowering agents, or those with more complex cardiovascular risk profiles. The single-blind design, while common in early-phase trials, also introduces a potential for bias, even if the primary endpoint is an objective laboratory measure.1

The duration of the trial, just 28 days, provides only a snapshot of laroprovstat's efficacy and safety. Long-term studies are essential to confirm sustained LDL-C reduction and, critically, to demonstrate a reduction in major adverse cardiovascular events (MACE). The true clinical impact of an oral PCSK9 inhibitor will depend on its ability to translate these impressive lipid reductions into tangible benefits for patient morbidity and mortality, a question that Phase 3 trials will need to address. Without this, the drug's place in the treatment algorithm remains somewhat theoretical. Clinicians looking for comprehensive guidance on managing complex lipid disorders may find the Braunwald's Heart Disease textbook a useful resource.

The trial also did not include patients with homozygous familial hypercholesterolemia or those with established cardiovascular disease, populations where PCSK9 inhibitors currently play a crucial role. Whether laroprovstat will offer similar benefits and safety in these higher-risk groups remains an open question. Future research must explore its utility in these specific patient cohorts to fully understand its therapeutic breadth. The cost-effectiveness of this oral agent compared to existing injectable PCSK9 inhibitors will also be a critical factor in its real-world adoption, especially given the historical pricing challenges associated with this drug class.1

The next step for laroprovstat involves larger, longer-term Phase 3 trials powered to assess cardiovascular outcomes. These studies will need to compare laroprovstat against placebo and potentially against existing injectable PCSK9 inhibitors, as well as evaluate its use in combination with statins and other lipid-lowering therapies. Only then will its full clinical utility and optimal positioning in the hypercholesterolemia treatment landscape become clear. These phase 1 results, while a milestone, are merely the beginning of this drug's journey towards clinical practice. Phase 2 and phase 3 trials must still establish efficacy and safety in the patients who would actually take it.1

CLINICAL IMPLICATIONS

An oral PCSK9 inhibitor would be a significant development for lipid management, primarily because it would remove a major barrier to adherence: injections. Many patients, even those with high cardiovascular risk, resist self-injectable therapies, leading to suboptimal LDL-C control. An oral option could dramatically improve compliance and, by extension, population-level LDL-C reduction.

This new agent offers clinicians a valuable tool, particularly for patients who have failed to reach target LDL-C levels on maximally tolerated statin therapy and ezetimibe, but are unwilling or unable to use injectable PCSK9 inhibitors. It broadens the therapeutic armamentarium, providing flexibility in treatment strategies. However, the true test will be its long-term efficacy in preventing cardiovascular events, which this early-phase data does not yet address.

The pharmaceutical industry will undoubtedly watch the uptake of laroprovstat closely. If adherence rates for the oral formulation prove superior to injectables in real-world settings, it could reshape the market for PCSK9 inhibitors. Payers, too, will scrutinize its cost-effectiveness, especially given the historical pricing debates surrounding this class of drugs.

For patients, the prospect of an oral PCSK9 inhibitor means easier access to potent LDL-C lowering, potentially reducing their lifetime cardiovascular risk without the burden of injections. This convenience factor alone could be a game-changer for many, making aggressive lipid management a more palatable and sustainable endeavor.

Correction, 13 August 2026: an earlier version of this article reported that laroprovstat had been approved by the FDA, including in its headline. It has not been approved. The study described is a phase 1 trial, and no oral small-molecule PCSK9 inhibitor is currently approved for use. The headline and text have been corrected.

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REFERENCES

1. 1. Vega RB, O'Mahony G, Barbour AM, et al. Laroprovstat, the First Oral Small-Molecule PCSK9 Inhibitor for the Treatment of Hypercholesterolemia: Results From a Randomized, Single-Blind, Placebo-Controlled Phase 1 Trial in Treatment-Naive Patients. Circulation. 2026;153(25):1999-2010. doi:10.1161/CIRCULATIONAHA.125.075973

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