The LEASH trial: rationale and study design for early rosuvastatin-ezetimibe combination compared with stepwise rosuvastatin in high/very-high cardiovascular risk

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Submitted: 2 October 2026; **Accepted:** 2 October 2026
Online publication: 3 October 2026

Arch Med Sci 2026; 22 (5): 2658–2666
DOI: https://doi.org/10.5114/aoms/240895
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Abstract

Introduction: Contemporary guidelines recommend early achievement of stringent low-density lipoprotein cholesterol (LDL-C) goals in patients at high or very high cardiovascular risk. The LEASH trial evaluates upfront rosuvastatin/ezetimibe combination therapy with a conventional stepwise intensification strategy in treatment-naïve patients.

Material and methods: LEASH is an international, prospective, multicentre, randomised, open-label trial. Treatment-naïve adults aged < 70 years are randomised 1 : 1 within country and risk strata. Arm 1 starts with rosuvastatin 20 mg/day with protocol-directed stepwise escalation; Arm 2 starts with rosuvastatin/ezetimibe 20/10 mg/day (single-pill combination, SPC) with subsequent intensification. Treatment is reassessed at 4, 8, and 12 weeks. The primary endpoint is proportion of patients achieving complete LDL-C goal at week 12, defined as ≥ 50% reduction from baseline plus LDL-C < 1.8 mmol/l (< 70 mg/dl) for high-risk or < 1.4 mmol/l (< 55 mg/dl) for very-high-risk patients. Secondary endpoints include early goal attainment at week 4 and 8, lipoprotein changes, adherence, between-arm differences, and safety. A full analysis set of 224 patients is planned. The trial is registered as EU CT 2023-504914-31-00.

Results: The LEASH trial is the first randomised controlled trial (RCT) to evaluate the early (4–12 weeks) efficacy and safety of an upfront SPC (rosuvastatin/ezetimibe) for LDL-C reduction and goal attainment in high and very-high cardiovascular risk patients. The results will inform not just whether combination therapy is effective in this population, but – critically – whether earlier initiation shortens the time to LDL-C goal attainment and, consequently, reduces the risk of first and subsequent cardiovascular events.

Conclusions: LEASH will assess whether upfront rosuvastatin/ezetimibe SPC therapy differs from conventional stepwise statin-based lipid-lowering intensification (with addition of ezetimibe as needed) in early (by 12 weeks) LDL-C reduction and goal achievement. Therapy adherence and early safety differences between the two approaches will also be assessed.

Key words: dyslipidaemia, rosuvastatin, ezetimibe, combination therapy, low-density lipoprotein cholesterol, cardiovascular risk.

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains a major cause of morbidity and mortality globally, which is substantially attributable to low-density lipoprotein cholesterol (LDL-C) [1, 2]. Genetic, epidemiological and randomised evidence indicates that cardiovascular risk reflects both the magnitude and duration of exposure to LDL-C [3, 4]. Clinical guidelines, and expert recommendations therefore, recommend early, intensive and sustained LDL-C reduction according to ASCVD risk [5–7]. In particular, the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines recommend both a ≥ 50% reduction in LDL-C from baseline and absolute LDL-C targets of < 1.8 mmol/l (< 70 mg/dl) and < 1.4 mmol/l (< 55 mg/dl) for individuals at high and very high cardiovascular risk, respectively [5]. In April 2021, the International Lipid Expert Panel (ILEP) recommended upfront combination lipid-lowering therapy with statins and ezetimibe – initially for acute coronary syndrome (ACS) and extreme-risk patients [8] and subsequently extended to all very-high-risk patients [9].

Despite increasingly effective lipid-lowering therapies (LLTs), guideline-recommended LDL-C goals remain difficult to achieve in routine clinical practice [10–13]. An important contributor to this implementation gap may be the traditional stepwise approach to lipid-lowering intensification – surprisingly still a common recommendation in many guidelines [14]. A high-intensity statin is commonly used as initial therapy, with dose optimisation followed by addition of ezetimibe when the LDL-C goal remains unmet [15]. Serial reassessment after each therapeutic step may delay goal attainment, particularly when statin monotherapy is unlikely to provide the required LDL-C reduction [14, 16]. Because of this ineffectiveness and the accumulating evidence, ILEP proposed earlier combination therapy – including upfront statin/ezetimibe – not only for post-event secondary prevention but also for patients with ASCVD to prevent first events [8, 17]. In 2025, this recommendation was extended in an expert-opinion paper to high- and very-high-risk primary prevention patients [18]. Randomised and observational studies, and meta-analyses, now broadly support this strategy, demonstrating greater LDL-C reductions and improved cardiovascular outcomes when ezetimibe is added to statin therapy [19–23].

To provide stronger evidence on upfront LLT in high-risk patients, LEASH compares two strategies in treatment-naïve individuals: a conventional stepwise approach (start high-intensity rosuvastatin and intensify if LDL-C goals are unmet) versus an upfront rosuvastatin/ezetimibe single-pill combination. The trial's primary objective is the proportion of patients achieving complete LDL-C response (≥ 50% reduction and risk-specific absolute LDL-C targets) at 4, 8, and 12 weeks, thereby evaluating both efficacy and time to goal attainment. The 2025 ESC/EAS focused update retained the 2019 LDL-C targets and emphasised timely treatment intensification [15], supporting the contemporary relevance of the LEASH design.

Material and methods

Study design

LEASH (*Lowering of LDL-C with rosuvastatin or single-pill combination rosuvastatin/ezetimibe in high/very high-risk patients with hyperlipidaemia*) is an international, multicentre, randomised, open-label, two-arm phase III/IV integrated trial conducted at 19 sites in Armenia, Croatia, Germany, Hungary, Poland and Serbia (Supplementary Material). Active treatment lasts 12 weeks, with screening, baseline/randomisation and follow-up assessments at 4, 8 and 12 weeks. The study is sponsored by Krka, d. d., Novo mesto, Slovenia, and registered as EU CT 2023-504914-31-00 (protocol KCT10/2022-LEASH).

Study population

Eligible participants are women and men aged ≥ 18 and < 70 years who are at high or very high cardiovascular risk, have LDL-C ≥ 1.8 mmol/l (≥ 70 mg/dl) or ≥ 1.4 mmol/l (≥ 55 mg/dl), respectively, and are treatment-naïve to lipid-lowering therapy (Table I; Supplementary Table SI). Patients must be ≥ 40 years if they are apparently healthy or have type 2 diabetes without established ASCVD. Cardiovascular risk is assessed using SCORE2 for apparently healthy participants [6], SCORE2-Diabetes for patients with type 2 diabetes without ASCVD [24], and guideline-defined criteria for those with established ASCVD (Table I).

The definitions of treatment-naïve status, treatment adherence, study-treatment discontinuation, and withdrawal are presented in the Supplementary Material.

Randomisation and masking

A stratified randomisation method is used. Before randomisation, eligible patients are classified as having high or very high cardiovascular risk. Within each CVD risk category/stratum and participating country, patients are randomised in a 1 : 1 ratio to a stepwise rosuvastatin-based strategy (Arm 1) or an upfront rosuvastatin/ezetimibe SPC strategy (Arm 2). Allocation is performed automatically through the electronic case report form (eCRF) system using a generated randomisation list. The study is open label, with

Table I. Principal eligibility criteria in the LEASH trial

Inclusion criteria	1	High or very high cardiovascular disease (CVD) risk with elevated LDL-C: LDL-C ≥ 1.8 mmol/l (≥ 70 mg/dl) in patients at high CVD risk or ≥ 1.4 mmol/l (≥ 55 mg/dl) in patients at very high CVD risk. Eligible risk categories comprise apparently healthy patients classified using SCORE2, patients with type 2 diabetes at high or very high CVD risk (SCORE2-Diabetes where applicable), and patients with established ASCVD.
	2	Treatment-naïve to all lipid-lowering therapy/therapies, defined as never having received lipid-lowering therapy or having received none for ≥ 4 weeks before Visit 1.
	3	Women or men aged ≥ 18 and < 70 years. Apparently healthy patients and patients with type 2 diabetes without ASCVD must be ≥ 40 years old.
	4	Provision of trial information, ability to understand the information according to the investigator judgement, and voluntary written informed consent.
	5	Written consent for collection, analysis, and processing of study data.
	6	Ability to comply with the trial protocol according to the investigator judgement.
Exclusion criteria	1	Known or suspected statin intolerance; hypersensitivity or previous adverse reactions to rosuvastatin, other HMG-CoA reductase inhibitors, ezetimibe, related lipid-lowering compounds, or relevant excipients.
	2	Pregnancy or lactation, or women of childbearing potential not using protocol-specified appropriate contraception.
	3	Current participation in another clinical trial.
	4	Acute disease, including severe infection, severe respiratory failure, exacerbation or uncontrolled chronic disease, major trauma, surgery, COVID-19, or post-COVID/long-COVID syndrome, within 30 days before screening.
	5	eGFR < 60 ml/min; suspected or documented moderate/severe hepatic dysfunction; active liver disease or persistent unexplained transaminase elevations, including AST or ALT > 3× upper limit of normal; or CK > 5× upper limit of normal at baseline.
	6	Diagnosed or suspected familial hypercholesterolaemia.
	7	Chronic kidney disease.
	8	Type 2 diabetes with diagnosed or suspected severe target-organ damage.
	9	Type 2 diabetes at moderate or low CVD risk according to SCORE2-Diabetes.
	10	Asian ancestry.
	11	Diagnosed or suspected secondary dyslipidaemia/hypercholesterolaemia, e.g. due to hypothyroidism.
	12	Previously diagnosed genetic polymorphism known to increase rosuvastatin exposure.
	13	Diagnosed or suspected myopathy, history of statin-associated myopathy or rhabdomyolysis, predisposing factors for myopathy/rhabdomyolysis, or personal/family history of hereditary muscular disorders.
	14	Concomitant treatment with protocol-specified contraindicated or clinically important interacting agents, including sofosbuvir/velpatasvir/voxilaprevir, ciclosporin, recent systemic fusidic acid, or other drugs substantially affecting rosuvastatin or ezetimibe exposure.
	15	LDL-C plasmapheresis within 2 months before screening or planned during the study.
	16	Surgical procedure planned during the study.
	17	Apparently healthy patients aged < 40 years and with systolic blood pressure ≥ 180 mm Hg, as specified in the protocol.
	18	Patients with type 2 diabetes without ASCVD aged < 40 years.

ASCVD – atherosclerotic cardiovascular disease, CK – creatine kinase, CVD – cardiovascular disease, eGFR – estimated glomerular filtration rate, LDL-C – low-density lipoprotein cholesterol.

no masking of patients or investigators. Patients remain in their assigned treatment strategy arm throughout the trial (Figure 1).

Treatment strategies

The trial evaluates two protocol-directed strategies. The conventional stepwise strategy (Arm 1) starts with rosuvastatin 20 mg/day, with protocol-directed intensification to rosuvastatin 40 mg/day and then rosuvastatin/ezetimibe 40/10 mg if the LDL-C goal is not achieved. The upfront combination strategy (Arm 2) starts with rosuvastatin/ezetimibe 20/10 mg/day, with intensification to rosuvastatin/ezetimibe 20/10 mg plus rosuvastatin 10 mg and then rosuvastatin/ezetimibe 40/10 mg (Figure 1; Table II). Patients achieving

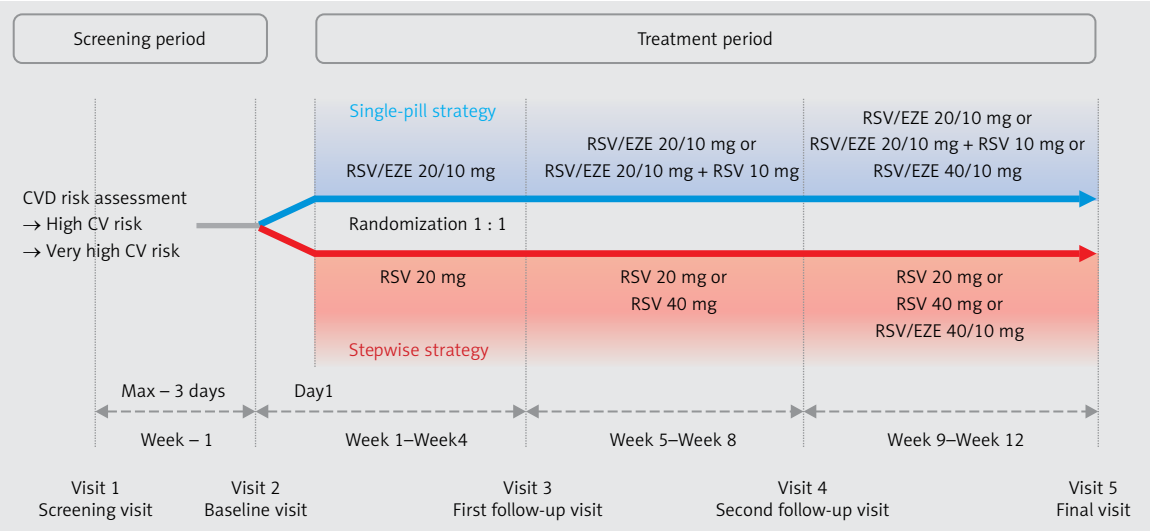


Figure 1. The LEASH trial design

the goal continue their current regimen if safe and tolerated. Treatment decisions at weeks 4 and 8 are based on safety/tolerability and attainment of the complete LDL-C goal, defined as both a ≥ 50% reduction from baseline and LDL-C < 1.8 mmol/l (< 70 mg/dl) for high-risk or < 1.4 mmol/l (< 55 mg/dl) for very-high-risk patients (Figure 1, Table II).

Study assessments

Clinical and laboratory assessments are performed at screening and during follow-up according to the prespecified study activities (Table III). Lipid measurements include total cholesterol, LDL-C, high density lipoprotein cholesterol (HDL-C), non-HDL-C and triglycerides. Safety assessments include CK, AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, serum creatinine and fasting glucose, together with office blood pressure, heart rate, concomitant medication and adverse events. Laboratory samples are obtained under fasting conditions and analyses are performed locally. Treatment adherence is assessed by study medication accountability, based on dispensed and returned study medication; a patient is considered adherent if at least 80% of prescribed doses have been administered.

Efficacy endpoints

The primary efficacy endpoint is the proportion of patients achieving the complete LDL-C goal at 12 weeks in each arm. Secondary endpoints include complete goal attainment at weeks 4 and 8;

Table II. Treatment strategies in the LEASH trial

Visit	Treatment stage	Arm 1: stepwise rosuvastatin strategy		Arm 2: upfront combination strategy	
2	Baseline	Rosuvastatin 20 mg/day		Rosuvastatin/ezetimibe (SPC) 20/10 mg/day	
3	Goal achieved	Continue rosuvastatin 20 mg/day		Continue rosuvastatin/ezetimibe 20/10 mg/day	
	Goal not achieved	Increase to rosuvastatin 40 mg/day or discontinue according to protocol criteria		Increase to rosuvastatin/ezetimibe 20/10 mg + rosuvastatin 10 mg/day or discontinue according to protocol criteria	
4	Goal achieved	Continue current rosuvastatin regimen		Continue current rosuvastatin/ezetimibe-based regimen	
	Goal not achieved	Goal not achieved on rosuvastatin 20 mg: increase to rosuvastatin 40 mg/day or discontinue	Goal not achieved on rosuvastatin 40 mg: increase to rosuvastatin/ezetimibe 40/10 mg/day or discontinue	Goal not achieved on rosuvastatin/ezetimibe 20/10 mg: increase to rosuvastatin/ezetimibe 20/10 mg + rosuvastatin 10 mg/day or discontinue	Goal not achieved on rosuvastatin/ezetimibe 20/10 mg + rosuvastatin 10 mg: increase to rosuvastatin/ezetimibe 40/10 mg/day or discontinue
5	Conclusion	Final efficacy and safety assessment		Final efficacy and safety assessment	

Complete LDL-C treatment goal: ≥ 50% reduction in LDL-C from baseline and LDL-C < 1.8 mmol/l (< 70 mg/dl) in high-risk patients or < 1.4 mmol/l (<55 mg/dl) in very-high-risk patients.

Table III. Schedule of study assessments

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening	**Baseline**	**~Week 4**	**~Week 8**	**~Week 12**
Timing	0–3 days before Visit 2	Day 0	28-34 days after Visit 2	28-34 days after Visit 3	28-34 days after Visit 4
Informed consent	X				
Demographics	X				
CVD risk assessment		X			
Eligibility verification		X			
Randomisation		X			
Study medication dispensing		X	X	X	
eCRF completion	X	X	X	X	X
Medical history and previous lipid-lowering therapy	X				
Physical examination, height, weight, BMI	X				
Concomitant medication review	X	X	X	X	X
Office blood pressure and heart rate	X	X	X	X	X
ECG	X[a]				
Full blood count	X[b]				
Serum sodium and potassium	X[b]				
CK, AST, ALT, ALP, GGT, serum creatinine	X[b]		X	X	X
Fasting glucose	X[b]		X		X
HbA1c	X[bc]				
Urine protein	X[b]			X[d]	X[d]
TC, LDL-C, HDL-C, non-HDL-C, triglycerides	X[b]		X	X	X
Pregnancy test, where applicable	X[b]		X	X	X
Efficacy assessment			X	X	X
Adverse-event review		X	X	X	X
Treatment-adherence assessment			X	X	X

[a] – An ECG performed within 6 months before Visit 1 may be used according to the protocol. [b] – Results may be assessed at Visit 1 or Visit 2 and constitute the baseline assessment as specified in the protocol. [c] – HbA1c is measured for patients with type 2 diabetes without ASCVD where required for SCORE2-Diabetes risk assessment. [d] – Urinary protein testing at Visits 4 and 5 is required when the rosuvastatin dose dispensed at the preceding visit was ≥ 30 mg.

≥ 50% LDL-C reduction; attainment of risk-specific LDL-C and non-HDL-C targets; absolute and relative changes in lipid parameters; adherence; and prespecified between-arm comparisons. Prespecified subgroup exploratory analyses of selected primary and secondary efficacy endpoints include analyses according to age, sex, prevention setting (primary/secondary prevention), type 2 diabetes and cardiovascular risk category (Table IV).

Safety endpoints

Safety endpoints include the incidence of drug-related adverse events (adverse reactions [ARs]) and serious adverse events (SAEs), changes in creatine kinase (CK), hepatic laboratory parameters and serum creatinine, changes in fasting glucose (FPG), and the incidence of adverse reactions according to reaction type.

Sample size and statistical analysis

The study was designed to estimate the primary endpoint with prespecified precision rather than to test a confirmatory between-arm superiority hypothesis. Assuming a 50% goal-attainment rate, 194 patients (97 per arm) provide an approximate 95% confidence interval of 40% to

Table IV. Prespecified exploratory subgroup analyses

Subgroup domain	Prespecified categories
Age	≥ 18 to < 50 years; ≥ 50 to < 70 years
Sex	Men; women
Prevention setting	Protocol-defined primary prevention; protocol-defined secondary prevention
Type 2 diabetes	With type 2 diabetes; without type 2 diabetes
Overall CVD risk	High CVD risk; very high CVD risk
Apparently healthy patients	All apparently healthy patients; high-risk apparently healthy patients; very-high-risk apparently healthy patients
Type 2 diabetes population	All patients with type 2 diabetes; high-risk patients with type 2 diabetes; very-high-risk patients with type 2 diabetes
Established ASCVD	Patients with established ASCVD

Protocol-defined primary prevention: apparently healthy patients without ASCVD and/or type 2 diabetes. Protocol-defined secondary prevention: patients with established ASCVD without type 2 diabetes. Apparently healthy patients: patients without established ASCVD, diabetes mellitus, chronic kidney disease, or familial hypercholesterolaemia, aged ≥ 40 years and with systolic blood pressure < 180 mm Hg.

60%. Allowing 10% dropout, 216 patients had been planned for randomisation; assuming 25% screening failure, 288 had been planned to be screened. Finally, 246 patients were screened, and a total of 224 patients fulfilled the protocol-defined criteria for the full analysis set (FAS).

The FAS comprises randomised patients who receive at least one dose of study medication and have a baseline and at least one post-baseline efficacy measurement. The primary analysis uses the FAS, consistent with ICH E9 intention-to-treat principles [25]. The per-protocol population (PP) includes patients completing the trial without major protocol violations and with required efficacy assessments; the safety analysis set (SAS) includes all randomised patients treated who took at least one dose of the study drug.

The primary endpoint are analysed based on the investigator-recorded binary variable (Yes/No) indicating achievement of the prespecified LDL-C treatment goal, defined as the absolute LDL-C target and a ≥ 50% reduction from baseline. Secondary endpoints related to LDL-C and non-HDL-C target attainment are derived directly from the measured lipid values. Values reported to two decimal places are rounded to one decimal place, and values reported in mg/dl are converted to mmol/l using the standard conversion formula. Thus, minor differences in target attainment rates between the primary and secondary endpoint analyses may reflect differences in the variables and calculation methods used. Primary and dichotomous secondary endpoints are summarised as proportions with 95% confidence intervals (CI). No formal between-arm hypothesis test is specified for the primary endpoint. Prespecified secondary between-arm comparisons will use the χ^2 or Fisher exact test, as appropriate. Numerical changes from baseline are summarised with 95% CI and assessed using paired-samples *t* tests or non-parametric alternatives, as appropriate. The nominal significance level is 0.05 with multiplicity adjustment for secondary outcomes. Missing observations will not be imputed in the primary analysis. No interim analysis is planned. Safety and exploratory analyses are descriptive.

Ethical and regulatory considerations

The trial is to be conducted in accordance with the protocol, applicable regulatory and ethics committee requirements, the principles of Good Clinical Practice, Regulation (EU) No. 536/2014 and other applicable regulatory requirements. Written informed consent is required before any study-specific screening procedure.

Patient confidentiality is maintained through coded study identifiers and the electronic data capture system. Study data are entered into a validated eCRF, and clinical monitoring and quality assurance procedures are performed according to the protocol and applicable Good Clinical Practice (GCP) requirements.

Results

The LEASH trial is the first randomised controlled trial to evaluate the early (4–12 weeks) efficacy and safety of an upfront single-pill combination (rosuvastatin/ezetimibe) for LDL-C reduction and goal attainment in patients at high or very high cardiovascular risk.

The results will determine whether upfront combination therapy should be considered in high- and very-high-risk patients in primary and secondary prevention by assessing whether it: (1) increases the likelihood of early attainment of combined (and individual) LDL-C goals, including specified LDL-C targets and ≥ 50% cholesterol reductions versus baseline; (2) produces greater early absolute LDL-C reductions; (3) favourably modifies other lipid parameters, including non-HDL-C; and (4) improves adherence and safety.

If LEASH meets its endpoints and is supported by outcome data and evidence of favourable atheroma plaque changes, these findings could prompt updates to European and US guidelines endorsing upfront combination lipid-lowering therapy as a Class I recommendation for all patients at high or very high cardiovascular risk.

Discussion

LEASH addresses a common practical problem in contemporary lipid management: not simply whether LDL-C can be reduced, but how rapidly patients at high or very high cardiovascular risk can reach complete guideline-recommended goals. Conventional treatment algorithms (too) often begin with statin monotherapy and intensify treatment only after reassessment of LDL-C response [5, 13]. Stepwise lipid-lowering escalation, however, may leave patients above target while awaiting treatment intensification and contribute to gaps between guideline-recommended and observed LDL-C levels [10–13]. In contrast, upfront statin/ezetimibe therapy may instead produce greater early LDL-C reductions and increase goal attainment from treatment onset [14, 17–22, 26].

LEASH therefore investigates the effectiveness of therapeutic strategies rather than fixed drug doses. Randomised comparisons of moderate-intensity statin plus ezetimibe with high-intensity statin monotherapy have demonstrated non-inferior cardiovascular outcomes [20] and superior LDL-C goal attainment [27], while observational evidence suggests that statin-ezetimibe combination therapy may be associated with further risk reductions when compared to statin monotherapy in selected populations [19–21]. To our knowledge, however, upfront combination therapy has not been directly compared with a stepwise escalation strategy in a randomised trial focused on early attainment of LDL-C goals. Serial assessments at 4, 8 and 12 weeks permit characterisation of both the trajectory and final extent of goal attainment. LEASH therefore provides evidence of the effectiveness of two feasible strategies, conventional stepwise strategy versus upfront combination therapy on the effectiveness and speed of LDL-C goal attainment in patients at high or very high cardiovascular risk.

A further feature is use of the complete ESC/EAS treatment goal rather than an absolute LDL-C target alone: patients must achieve both a ≥ 50% reduction and the risk-specific absolute target [15]. This is particularly relevant because observational studies may assess only absolute LDL-C targets [10–13]. The treatment-naïve population permits percentage reduction to be assessed from a defined baseline, while inclusion of apparently healthy high- or very-high-risk individuals, patients with type 2 diabetes [28] and patients with established ASCVD may provide exploratory assessment of treatment response in clinically diverse populations.

Several design characteristics should be considered when interpreting the eventual findings. First, the open-label design may influence adherence and adverse-event reporting, although efficacy endpoints are objective laboratory measurements. Second, the study is sized for precision of within-arm goal-attainment estimates rather than confirmatory superiority. Third, the 12-week duration cannot address cardiovascular outcomes or long-term safety, persistence and adherence. Fourth, local laboratory testing, while resembling routine clinical practice, may introduce inter-laboratory variability. Finally, the exclusion of patients with chronic kidney disease, familial hypercholesterolaemia and statin intolerance limit generalisability.

Conversely, several features strengthen the clinical relevance of the trial. Inclusion of treatment-naïve patients and protocol-directed adjustment to risk-specific LDL-C goals strengthen the interpretation of treatment response and replicate a decision pathway relevant to clinical practice. Stratified randomisation and the international multicentre design also permit evaluation across different healthcare settings, broadening the geographical context in which contemporary LDL-C treatment strategies are prospectively evaluated. The strive for early attainment of risk-specific LDL-C goals aligns with the 2025 ESC/EAS dyslipidaemia guidelines focused update [15], and expert opinion recommendations [17, 18], thus supporting the contemporary relevance of the LEASH design.

In conclusion, the LEASH trial is a randomised, international, multicentre trial designed to evaluate two clinically relevant lipid-lowering strategies in patients at high and very high cardiovascular risk. By assessing complete LDL-C goal attainment at 4, 8 and 12 weeks, it focuses on both the timing and extent of lipid control and may inform the ongoing transition from a predominantly stepwise lipid-lowering strategy toward earlier individualised single-pill combination therapy.

Acknowledgments

Trial registration:_The study is registered in the Clinical Trials Information System (CTIS) under trial number 2023-504914-31-00 (protocol KCT10/2022-LEASH).

Funding

The authors declare that this study was supported by funding from Krka, d. d., Novo mesto. The funder contributed to the study design, data collection, and independent verification of the statistical analyses to ensure accuracy.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable national regulatory requirements. The study protocol, informed consent forms, and related study documents were approved by the appropriate ethics committees and regulatory authorities before study initiation. Written informed consent was obtained from all participants before any study-specific procedures were performed.

Conflict of interest

Borut Jug, Parounak Zelveian, Ivan Pećin, Martin Bergmann, László Márk/Laszlo Mark, and Dragan Simić declare no personal competing interests related to this work. Maciej Banach has received research grant(s)/support from Amgen, Daiichi Sankyo, Mylan/Viatris, and Sanofi, and has served as a consultant/received speakers fee from Adamed, Amgen, Daiichi-Sankyo, KRKA, Lilly, Mylan/Viatris, NewAmsterdam, Novartis, Novo-Nordisk, Polpharma, Sanofi, Servier, Sobe, Teva, and Zentiva (not related to current analysis).

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