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Oral Muvalaplin for Lowering of Lipoprotein(a)
A Randomized Clinical Trial

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IMPORTANCE Muvalaplin inhibits lipoprotein(a) formation. A 14-day phase 1 study demonstrated that muvalaplin was well tolerated and reduced lipoprotein(a) levels up to 65%. The effect of longer administration of muvalaplin on lipoprotein(a) levels in individuals at high cardiovascular risk remains uncertain.

OBJECTIVES To determine the effect of muvalaplin on lipoprotein(a) levels and to assess safety and tolerability.

DESIGN, SETTING, AND PARTICIPANTS Phase 2, placebo-controlled, randomized, double-blind trial enrolling 233 participants with lipoprotein(a) concentrations of 175 nmol/L or greater with atherosclerotic cardiovascular disease, diabetes, or familial hypercholesterolemia at 43 sites in Asia, Europe, Australia, Brazil, and the United States between December 10, 2022, and November 22, 2023.

INTERVENTIONS Participants were randomized to receive orally administered muvalaplin at dosages of 10 mg/d (n = 34), 60 mg/d (n = 64), or 240 mg/d (n = 68) or placebo (n = 67) for 12 weeks.

MAIN OUTCOMES AND MEASURES The primary end point was the placebo-adjusted percentage change from baseline in lipoprotein(a) molar concentration at week 12, using an assay to measure intact lipoprotein(a) and a traditional apolipoprotein(a)-based assay. Secondary end points included the percentage change in apolipoprotein B and high-sensitivity C-reactive protein.

RESULTS The median age of study participants was 66 years; 33% were female; and 27% identified as Asian, 4% as Black, and 66% as White. Muvalaplin resulted in placebo-adjusted reductions in lipoprotein(a) of 47.6% (95% CI, 35.1%-57.7%), 81.7% (95% CI, 78.1%-84.6%), and 85.8% (95% CI, 83.1%-88.0%) for the 10-mg/d, 60-mg/d, and 240-mg/d dosages, respectively, using an intact lipoprotein(a) assay and 40.4% (95% CI, 28.3%-50.5%), 70.0% (95% CI, 65.0%-74.2%), and 68.9% (95% CI, 63.8%-73.3%) using an apolipoprotein(a)-based assay. Dose-dependent reductions in apolipoprotein B were observed at 8.9% (95% CI, −2.2% to 18.8%), 13.1% (95% CI, 4.4%-20.9%), and 16.1% (95% CI, 7.8%-23.7%) at 10 mg/d, 60 mg/d, and 240 mg/d, respectively. No change in high-sensitivity C-reactive protein was observed. No safety or tolerability concerns were observed at any dosage.

CONCLUSIONS AND RELEVANCE Muvalaplin reduced lipoprotein(a) measured using intact lipoprotein(a) and apolipoprotein(a)-based assays and was well tolerated. The effect of muvalaplin on cardiovascular events requires further investigation.

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Visual Abstract

Supplemental content

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Genomic[1-3] and cohort[4] studies have demonstrated that higher lipoprotein(a) levels are associated with an increased risk of both atherosclerotic cardiovascular disease and calcific aortic valve stenosis.[5,6] Lipoprotein(a) is genetically determined, and lipoprotein(a) levels are reached early in life and then remain largely stable.[5,6] The pathogenesis of atherosclerosis due to lipoprotein(a) is attributed to proatherogenic, proinflammatory, and possibly prothrombotic effects.[7]

Whether lipoprotein(a) is a modifiable risk factor, who benefits from lipoprotein(a) lowering, and the degree of lipoprotein(a) lowering needed to reduce cardiovascular events remain unknown. Therapeutic options for patients with elevated lipoprotein(a) levels are currently limited. Genetic epidemiology studies suggest that large reductions of 85 to 250 nmol/L may be needed to lower cardiovascular risk,[3,8,9] and there is currently no pharmacotherapy approved for lowering lipoprotein(a) levels. Apheresis has been used to lower lipoprotein(a) but it is invasive, time-consuming, and costly.[10,11]

Lipoprotein(a) includes an apolipoprotein B-containing low-density lipoprotein (LDL)-like particle covalently bound to the apolipoprotein(a) molecule.[7] Nucleic acid-based therapeutics that lower lipoprotein(a) by preventing apolipoprotein(a) transcription are in clinical development. A parenterally administered antisense oligonucleotide lowered lipoprotein(a) by approximately 80%,[12] and parenterally administered small interfering RNA-based therapies have shown greater than 90% reductions.[13-16]

Muvalaplin is the first agent developed to lower lipoprotein(a) levels by targeting assembly of the lipoprotein(a) particle, rather than apolipoprotein(a) expression. An oral therapy, muvalaplin, disrupts the initial noncovalent interaction between apolipoprotein(a) and apolipoprotein B, inhibiting subsequent disulfide bond formation and preventing lipoprotein(a) formation.[17] A phase 1 trial of healthy participants with and without elevated lipoprotein(a) levels demonstrated good tolerability and reductions in lipoprotein(a) levels up to 65% after 14 days of muvalaplin administration.[18] The assay used in that trial, and all commercially available assays that measure lipoprotein(a), are antibody-based assays that measure apolipoprotein(a) levels. Given that apolipoprotein(a) is predominantly in lipoprotein(a) particles, apolipoprotein(a)-based assays accurately reflect serum lipoprotein(a) levels in the general population.[19] However, in the presence of a lipoprotein(a) inhibitor such as muvalaplin, an apolipoprotein(a)-based assay may overestimate serum lipoprotein(a) concentrations, as it will measure apolipoprotein(a) in intact lipoprotein(a) particles, free apolipoprotein(a), and apolipoprotein(a) bound to muvalaplin. The KRAKEN study evaluated the effects and tolerability of a range of muvalaplin doses on serum lipoprotein(a) concentrations after 12 weeks of treatment in adults with elevated lipoprotein(a) levels and at high risk of cardiovascular events using both a traditional apolipoprotein(a)-based assay and a novel assay that detects intact lipoprotein(a) particles.

Key Points

Question Can the oral small molecule lipoprotein(a) inhibitor muvalaplin reduce lipoprotein(a) levels in patients with elevated lipoprotein(a) concentrations at high risk of cardiovascular events?

Findings In this phase 2 study, patients with lipoprotein(a) concentrations of 175 nmol/L or greater with established cardiovascular disease, diabetes, or familial hypercholesterolemia were randomized to receive treatment with placebo or muvalaplin at dosages of 10 mg/d, 60 mg/d, or 240 mg/d for 12 weeks. Muvalaplin produced placebo-adjusted reductions in lipoprotein(a) by up to 85.8% using an intact lipoprotein(a) assay and by up to 70.0% using an apolipoprotein(a) assay. Muvalaplin administration was not associated with safety or tolerability concerns.

Meaning Muvalaplin was well tolerated and produced substantial reductions in lipoprotein(a) levels in patients at high risk of cardiovascular events. The impact on cardiovascular events requires further investigation.

Methods

Study Design

This phase 2, randomized, double-blind, placebo-controlled trial was conducted at 43 sites in Australia, Brazil, China, Germany, Hungary, Japan, the Netherlands, and the United States. The study was sponsored and designed by Eli Lilly and Company in consultation with the academic authors. The study protocol was approved by an independent ethics committee. All participants provided written informed consent. The study protocol and statistical analysis plan are available in Supplement 1 and Supplement 2.

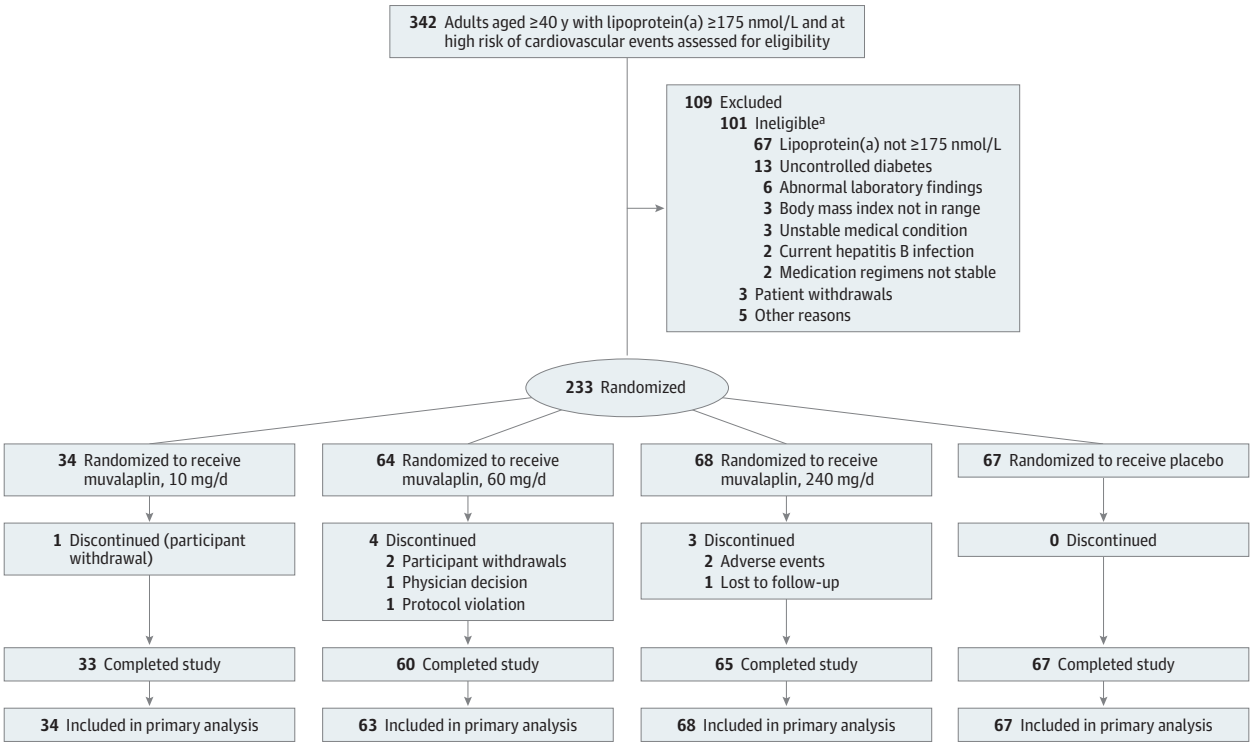
Study Population

Eligible participants were adults aged 40 years or older at high risk of cardiovascular events and with serum lipoprotein(a) concentrations of 175 nmol/L or greater. High cardiovascular risk was defined as history of coronary artery disease, ischemic stroke, or peripheral arterial disease; type 2 diabetes; or familial hypercholesterolemia. Participants receiving treatment with lipid-lowering medications or hormone therapies could be enrolled if they had been following a stable drug regimen for 4 weeks prior and were expected to continue that regimen during the trial. Exclusion criteria included uncontrolled diabetes or hypertension, estimated glomerular filtration rate less than 30 mL/min/1.73 m^2, body mass index less than 18.5 or greater than 40 (calculated as weight in kilograms divided by height in meters squared), any cardiovascular event or surgery in the past 3 months, and other conditions indicating an unstable medical state.

Treatment Protocol

Participants were randomly assigned to receive muvalaplin, 10, 60, or 240 mg, or placebo in a 1:2:2:2 ratio, administered as 4 oral tablets once daily for 12 weeks (eFigure 1 in Supplement 3). Randomization was performed using an interactive

Figure 1. Participant Flow in the KRAKEN Trial



[a]Other ineligible participants included single cases of judged unreliable, uncontrolled hypertension, not at high risk of cardiovascular event, malignancy within prior 5 years, and younger than 40 years.

web response system and stratified by country and lipoprotein(a) concentration (<275 nmol/L or ≥275 nmol/L). Participants underwent fasting visits on day 0 and at weeks 1, 2, 4, 8, and 12 during the treatment period, as well as a posttreatment visit 4 weeks after the last dose. Adverse events, concomitant medications, lipoprotein(a) levels by apolipoprotein (a)-based assay, high-sensitivity C-reactive protein (hs-CRP), and plasminogen activity were measured at each visit. Intact lipoprotein(a) and oxidized phospholipid levels were assessed from stored samples in a blinded fashion from baseline and weeks 4 and 12. Levels of apolipoprotein B and lipid panels were evaluated at baseline and weeks 4, 8, and 12. Race and ethnicity were collected by self-report.

Outcome Measures

The primary end point was the percentage change in lipoprotein(a) from baseline to week 12 in each muvalaplin dosage group compared with the placebo group. Lipoprotein(a) was quantified using both a commercially available apolipoprotein(a)-based assay (Randox Laboratories) that measures the serum molar concentration of total apolipoprotein(a) using polyclonal antiapolipoprotein(a) antibodies (RX series LP 3403) and a novel intact lipoprotein(a) assay that measures the serum molar concentration of intact lipoprotein(a) particles. This intact lipoprotein(a) assay uses a sandwich format including an antiapolipoprotein B antibody and an isoform-insensitive antiapolipoprotein(a) antibody to detect the concentration of intact lipoprotein(a) particles containing apolipoprotein(a) bound to apolipoprotein B.

Secondary end points included the proportion of participants achieving a lipoprotein(a) concentration of less than 125 nmol/L at week 12, percentage changes in apolipoprotein B and hs-CRP concentrations, and muvalaplin pharmacokinetics. Changes in plasminogen activity and LDL cholesterol (LDL-C) were prespecified exploratory end points. Oxidized phospholipid levels associated with either apolipoprotein B or apolipoprotein(a) were measured by immunoassay using capture antibodies to apolipoprotein B (MB47) and apolipoprotein(a) (LPA4), with a secondary murine monoclonal antibody, EO6, recognizing the phosphocholine head group of oxidized but not native phospholipids.[20-23] Safety was evaluated via collection of adverse events, vital signs, and safety laboratory values. Counts and percentages of adverse events, including treatment-emergent adverse events, major adverse cardiovascular events, and serious adverse events, were summarized by treatment group. Major adverse cardiovascular events and deaths were adjudicated by an independent committee of physicians blinded to treatment assignment.

Sample Size Determination

The sample size determination was based on the primary end point, percentage change from baseline at week 12 in lipoprotein(a). Approximately 233 patients were expected to be randomly assigned in a 1:2:2:2 ratio to muvalaplin at dosages of

Table 1. Baseline Participant Characteristics

Characteristics	Muvalaplin 10 mg/d (n = 34)	Muvalaplin 60 mg/d (n = 64)	Muvalaplin 240 mg/d (n = 68)	Placebo (n = 67)
Age, median (IQR), y	66.5 (58.0-71.0)	67.0 (59.5-71.0)	66.0 (58.0-70.5)	63.0 (55.0-70.0)
Sex, No. (%)				
Female	11 (32.4)	22 (34.4)	24 (35.3)	19 (28.4)
Male	23 (67.6)	42 (65.6)	44 (64.7)	48 (71.6)
Race and ethnicity, No. (%)				
Asian	9 (26.5)	17 (26.6)	19 (27.9)	18 (26.9)
Black	2 (5.9)	5 (7.8)	1 (1.5)	1 (1.5)
Hispanic or Latino	4 (11.8)	11 (17.2)	10 (14.7)	9 (13.4)
Native Hawaiian or Other Pacific Islander	1 (2.9)	0	0	0
White	22 (64.7)	41 (64.1)	45 (66.2)	45 (67.2)
Multiple	0	1 (1.6)	3 (4.4)	3 (4.5)
Comorbidities, No. (%)				
Coronary artery disease	27 (79.4)	49 (76.6)	50 (73.5)	44 (65.7)
Myocardial infarction	16 (47.1)	26 (40.6)	25 (36.8)	24 (35.8)
Type 2 diabetes	11 (32.4)	24 (37.5)	28 (41.2)	15 (22.4)
Familial hypercholesterolemia	2 (5.9)	6 (9.4)	10 (14.7)	7 (10.4)
Cerebrovascular accident	2 (5.9)	2 (3.1)	5 (7.4)	4 (6.0)
Concomitant medications, No. (%)[a]				
Lipid-modifying agents	34 (100)	58 (90.6)	66 (97.1)	60 (89.6)
Statins	34 (100)	56 (87.5)	62 (91.2)	60 (89.6)
Ezetimibe	14 (41.2)	24 (37.5)	31 (45.6)	29 (43.3)
PCSK9 inhibitors	1 (2.9)	7 (10.9)	9 (13.2)	5 (7.5)
Antithrombotic agents	30 (88.2)	56 (87.5)	57 (83.8)	58 (86.6)
β-Blocking agents	20 (58.8)	39 (60.9)	33 (48.5)	31 (46.3)

Abbreviation: PCSK9, proprotein convertase subtilisin/kexin type 9.

[a] Concomitant medication data summarize use throughout entire study period. Lipid-modifying agents include statins, ezetimibe, PCSK9 inhibitors (evolocumab, alirocumab, inclisiran), and fibrates. Antithrombotic agents include aspirin and all anticoagulants.

10 mg/d, 60 mg/d, and 240 mg/d or placebo, respectively. Assuming a 10% dropout rate, an SD of 20%, and a 2-sided α = .05, the completers for each treatment group were expected to provide greater than 99% power to detect a treatment difference of 60% reduction for the primary end point of muvalaplin compared with placebo.

Statistical Analysis

The prespecified primary efficacy estimand was an evaluation of the mean treatment effect of muvalaplin relative to placebo in a population that would adhere to study treatment, without initiating other medications known to impact lipoprotein(a) levels. All participants exposed to at least 1 dose of study intervention were included in the primary analysis, excluding data after permanent study drug discontinuation or initiation of new lipoprotein(a)-modifying medications. Continuous end points were analyzed using a mixed model for repeated measures that included the continuous baseline value, randomization strata, treatment, visit, and a treatment-by-visit interaction as covariates. Continuous variables were log-transformed prior to analysis as needed to satisfy the normality assumption. For binary end points derived from a continuous variable, missing values of the continuous variable were imputed under the missing-at-random assumption prior to dichotomization. Binary end points were then analyzed using a logistic regression model that included the corresponding continuous baseline value, randomization strata, and treatment as covariates. A secondary treatment regimen estimand was prespecified for the primary end point, which assessed the mean treatment effect regardless of treatment discontinuation or initiation of lipoprotein(a)-modifying medication. The treatment regimen estimand analyzed a modified intention-to-treat population including all participants exposed to at least 1 dose of study intervention. Safety assessments were performed for all exposed participants. Treatment comparisons for all end points were performed at the full significance level of $P < .05$. R version 3.4.0 (R Foundation) was used for analyses.

Results

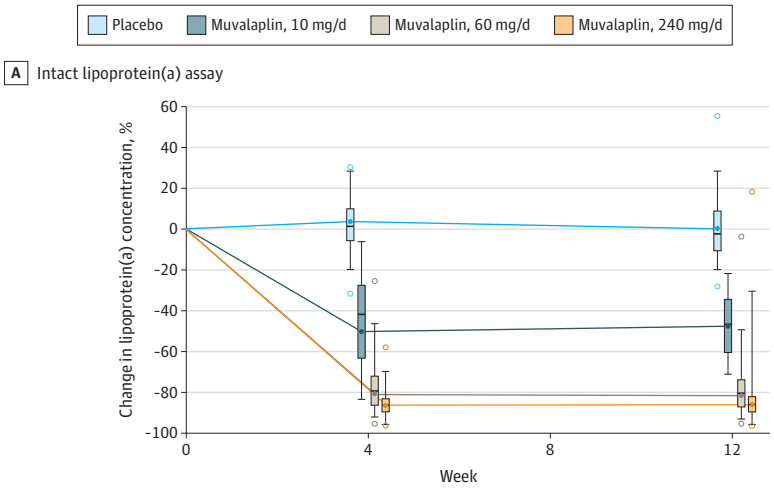
Patient Characteristics

The dispositions of patients screened and randomized are summarized in **Figure 1**. From December 10, 2022, to November 22, 2023, 233 participants were randomly assigned and treated with 10 mg/d (n = 34), 60 mg/d (n = 64), or 240 mg/d (n = 68) of muvalaplin or placebo (n = 67). Of these, 33, 60, and 65 participants in the 10-mg/d, 60-mg/d, and 240-mg/d groups, respectively, and 67 participants in the placebo group

Table 2. Primary and Secondary End Points

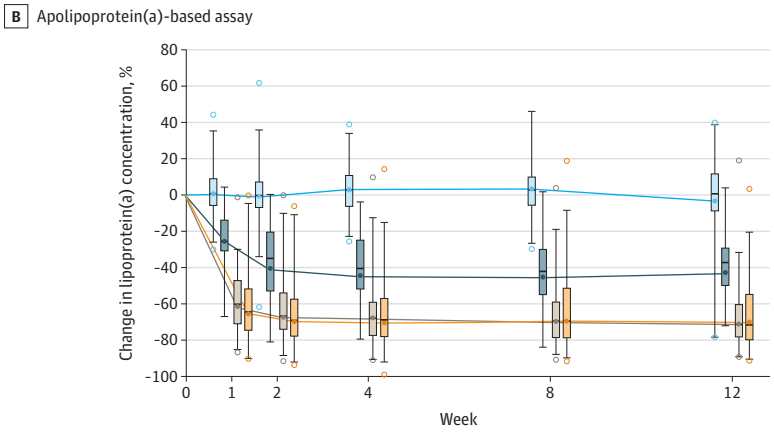
End points	Least-squares mean (95% CI)			
	Muvalaplin			
	10 mg/d (n =34)	60 mg/d (n = 63)	240 mg/d (n = 68)	Placebo (n = 67)
Primary end point				
Lipoprotein(a) measured by intact lipoprotein(a) assay				
Baseline, nmol/L	211.0 (174.0 to 248.0) [n = 27]	198.2 (173.2 to 223.3) [n = 52]	223.5 (196.1 to 251.0) [n = 55]	234.2 (205.9 to 262.5) [n = 57]
Week 12, nmol/L	113.6 (93.1 to 134.1) [n = 23]	39.8 (34.5 to 45.0) [n = 45]	30.9 (26.9 to 34.8) [n = 47]	216.9 (189.7 to 244.0) [n = 49]
Absolute change, nmol/L	−101.8 (−122.2 to −81.4)	−175.3 (−180.5 to −170.1)	−184.2 (−188.1 to −180.2)	1.0 (−26.0 to 28.1)
% Change	−47.4 (−56.0 to −37.0)	−81.6 (−83.8 to −79.0)	−85.7 (−87.4 to −83.8)	0.5 (−11.4 to 13.9)
Placebo-adjusted % change	−47.6 (−57.7 to −35.1)	−81.7 (−84.6 to −78.1)	−85.8 (−88.0 to −83.1)	
Lipoprotein(a) measured by apolipoprotein(a)-based assay				
Baseline, nmol/L	258.2 (229.2 to 287.1)	238.8 (219.0 to 258.6) [n = 62]	259.4 (238.9 to 280.0)	252.9 (232.7 to 273.1)
Week 12, nmol/L	145.2 (123.0 to 167.4) [n = 29]	73.2 (64.9 to 81.5) [n = 56]	75.7 (67.4 to 84.0) [n = 57]	243.5 (217.0 to 270.0) [n = 60]
Absolute change, nmol/L	−105.5 (−127.6 to −83.5)	−177.1 (−185.3 to −168.8)	−174.5 (−182.8 to −166.3)	−7.9 (−34.2 to 18.4)
% Change	−42.3 (−50.4 to −32.7)	−70.9 (−74.0 to −67.4)	−69.9 (−73.0 to −66.4)	−3.2 (−13.1 to 8.0)
Placebo-adjusted % change	−40.4 (−50.5 to −28.3)	−70.0 (−74.2 to −65.0)	−68.9 (−73.3 to −63.8)	
Secondary end points				
Apolipoprotein B				
Baseline, mg/dL	79.5 (70.9 to 88.1) [n = 33]	74.2 (68.4 to 80.1) [n = 62]	77.3 (71.3 to 83.3) [n = 64]	75.5 (69.8 to 81.2)
Week 12, mg/dL	68.0 (61.5 to 74.5) [n = 29]	64.9 (60.4 to 69.5) [n = 56]	62.6 (58.3 to 66.9) [n = 57]	74.7 (69.6 to 79.7) [n = 60]
Absolute change, mg/dL	−8.0 (−14.5 to −1.5)	−11.0 (−15.6 to −6.5)	−13.4 (−17.7 to −9.0)	−1.3 (−6.3 to 3.7)
% Change	−10.5 (−18.7 to −1.5)	−14.5 (−20.3 to −8.3)	−17.6 (−23.0 to −11.7)	−1.7 (−8.1 to 5.2)
Placebo-adjusted % change	−8.9 (−18.8 to 2.2)	−13.1 (−20.9 to −4.4)	−16.1 (−23.7 to −7.8)	
High-sensitivity C-reactive protein				
Baseline, mg/L	1.5 (0.9 to 2.1)	1.0 (0.7 to 1.3) [n = 62]	0.8 (0.6 to 1.1)	1.0 (0.7 to 1.3)
Week 12, mg/L	1.2 (0.8 to 1.6) [n = 29]	1.0 (0.8 to 1.2) [n = 56]	0.9 (0.7 to 1.1) [n = 57]	0.9 (0.7 to 1.1) [n = 58]
Absolute change, mg/dL	0.2 (−0.2 to 0.6)	0 (−0.3 to 0.2)	−0.2 (−0.4 to 0)	−0.1 (−0.3 to 0.1)
% Change	21.9 (−11.9 to 68.5)	−2.4 (−23.0 to 23.6)	−15.4 (−32.8 to 6.6)	−9.9 (−28.4 to 13.4)
Placebo-adjusted % change	35.3 (−8.6 to 100.3)	8.3 (−21.6 to 49.7)	−6.1 (−31.9 to 29.5)	
Participants with lipoprotein(a) <125 nmol/L at week 12, %				
Intact lipoprotein(a) assay	64.2 (45.3 to 79.6)	95.9 (86.8 to 98.8)	96.7 (85.7 to 99.3)	6.0 (2.3 to 14.9)
Apolipoprotein(a)-based assay	38.9 (24.8 to 55.1)	81.9 (71.2 to 89.3)	77.4 (66.7 to 85.4)	3.6 (0.9 to 13.2)

Figure 2. Percentage Change in Lipoprotein(a) Concentration Measured by Intact Lipoprotein(a) Assay and Apolipoprotein(a)-Based Assay



No. of patients

Placebo	57	54	49
Muvalaplin, 10 mg/d	27	27	23
Muvalaplin, 60 mg/d	52	51	45
Muvalaplin, 240 mg/d	55	55	47



No. of patients

Placebo	67	66	65	64	65	60
Muvalaplin, 10 mg/d	34	34	32	33	32	29
Muvalaplin, 60 mg/d	62	60	60	61	60	56
Muvalaplin, 240 mg/d	68	67	68	64	61	57

Data are presented as least-squares means (solid dots), medians (lines), IQRs (boxes), 2.5th and 97.5th percentiles (whiskers), and outliers (open circles). Intact lipoprotein(a) was not measured at weeks 1, 2, or 8. Intact lipoprotein(a) was not measured in 30 patients in China, as storage of samples was not permitted.

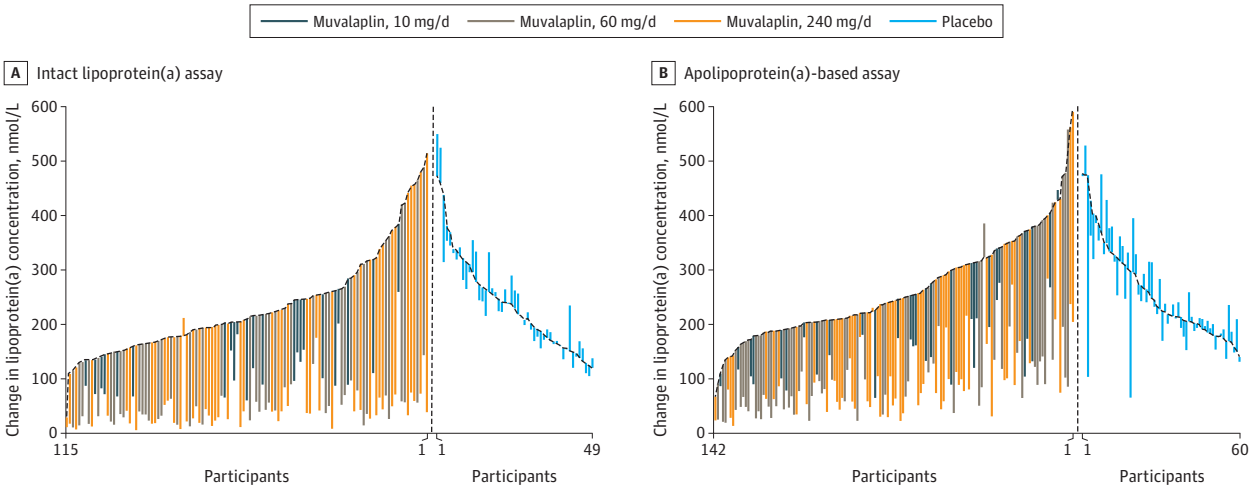
completed the study. The demographics and concomitant medication use of participants were broadly similar between the study groups (**Table 1**). The median age was 66 years; 33% were female; and 27% identified as Asian, 4% as Black, and 66% as White. A history of coronary artery disease was present in 73.0%, 33.5% had diabetes, and 10.7% had familial hypercholesterolemia. The most frequently used concomitant medications were statins (91.0%), antithrombotic agents (86.3%), and β-blockers (52.8%).

Biochemical parameters at baseline are summarized in **Table 2**. Median baseline lipoprotein(a) levels for the overall cohort were 216.8 nmol/L using the intact lipoprotein(a) assay and 246.5 nmol/L using the apolipoprotein(a) assay. The median level of LDL-C was 73.5 mg/dL, apolipoprotein B was 76.0 mg/dL, and hs-CRP was 0.9 mg/L. There were no differences in lipid parameters or hs-CRP between study groups at baseline.

Primary End Point

After 12 weeks of treatment, reductions in lipoprotein(a) were observed in all muvalaplin dosage groups, but not in the placebo group, using both assays (Table 2, **Figure 2**; eFigure 2 in Supplement 3). Percentage changes in lipoprotein(a) using the intact assay were 0.5% (95% CI, −11.4% to 13.9%) with placebo and −47.4% (95% CI, −56.0% to −37.0%), −81.6% (95% CI, −83.8% to −79.0%), and −85.7% (95% CI, −87.4% to −83.8%) with 10 mg/d, 60 mg/d, and 240 mg/d of muvalaplin, respectively. The intact lipoprotein(a) assay demonstrated placebo-adjusted reductions in lipoprotein(a) by 47.6% (95% CI, 35.1%-57.7%) in the 10-mg/d muvalaplin

Figure 3. Absolute Change in Lipoprotein(a) Concentration Among Individual Participants at Week 12 Measured by Intact Lipoprotein(a) Assay and Apolipoprotein(a)-Based Assay



Waterfall plots demonstrate individual absolute changes from baseline in lipoprotein(a) concentration at week 12 with placebo and different doses of muvalaplin. Intact lipoprotein(a) was not measured in 30 patients in China, as storage of samples was not permitted.

group, 81.7% (95% CI, 78.1%-84.6%) in the 60-mg/d muvalaplin group, and 85.8% (95% CI, 83.1%-88.0%) in the 240-mg/d muvalaplin group. Percentage changes in lipoprotein(a) using the apolipoprotein(a) assay were −3.2% (95% CI, −13.1% to 8.0%) with placebo and −42.3% (95% CI, −50.4% to −32.7%), −70.9% (95% CI, −74.0% to −67.4%), and −69.9% (95% CI, −73.0% to −66.4%) with 10 mg/d, 60 mg/d, and 240 mg/d of muvalaplin, respectively. The apolipoprotein(a) assay demonstrated placebo-adjusted reductions in lipoprotein(a) of 40.4% (95% CI, 28.3%-50.5%) in the 10-mg/d muvalaplin group, 70.0% (95% CI, 65.0%-74.2%) in the 60-mg/d muvalaplin group, and 68.9% (95% CI, 63.8%-73.3%) in the 240-mg/d muvalaplin group. Waterfall plots of individual percentage changes from baseline in lipoprotein(a) concentrations at week 12, using either assay, demonstrated limited interpatient variability in response (**Figure 3**; eFigure 3 in Supplement 3). Intact lipoprotein(a) measurements were not available for 30 patients in China, as storage of samples was not allowed. A sensitivity analysis of the effects of muvalaplin on lipoprotein(a) using the apolipoprotein(a) assay excluding patients from China demonstrated no differences from the overall findings (eTable 1 in Supplement 3).

Secondary End Points

Using the intact lipoprotein(a) assay, the percentages of participants achieving a lipoprotein(a) concentration of less than 125 nmol/L at week 12 were 64.2%, 95.9%, and 96.7% in the 10-mg/d, 60-mg/d, and 240-mg/d muvalaplin groups, respectively, and 6.0% in the placebo group (Table 2; eFigure 4 in Supplement 3). Using the apolipoprotein(a) assay, the percentages of participants achieving a lipoprotein(a) concentration of less than 125 nmol/L were 38.9%, 81.9%, and 77.4% in the 10-mg/d, 60-mg/d, and 240-mg/d muvalaplin groups, respectively, and 3.6% in the placebo group. Similar effects of muvalaplin on placebo-adjusted changes in lipoprotein(a) and the percentage of patients achieving a lipoprotein(a) less than 125 nmol/L at week 12 were observed using a modified intention-to-treat analysis (eTable 2 in Supplement 3).

Apolipoprotein B levels were reduced with muvalaplin in a dose-responsive fashion, with placebo-corrected changes at week 12 of −8.9% (95% CI, −18.8% to 2.2%) at 10 mg/d, −13.1% (95% CI, −20.9% to −4.4%) at 60 mg/d, and −16.1% (95% CI, −23.7% to −7.8%) at 240 mg/d. No statistically significant changes in hs-CRP concentrations at week 12 were observed in any treatment group.

Exploratory End Points

Placebo-adjusted percentage changes in oxidized phospholipid apolipoprotein B levels at week 12 were −35.0% (95% CI, −56.0% to −3.9%%), −67.2% (95% CI, −76.3% to −54.5%), and −58.8% (95% CI, −70.3% to −43.0%) in the 10-mg/d, 60-mg/d, and 240-mg/d muvalaplin groups, respectively. Similarly, placebo-adjusted percentage changes in oxidized phospholipid apolipoprotein(a) levels at week 12 were −23.7% (95% CI, −43.0% to 2.2%), −70.9% (95% CI, −77.2% to −62.8%), and −73.0% (95% CI, −78.8% to −65.7%) in the 10-mg/d, 60-mg/d, and 240-mg/d muvalaplin groups, respectively (eFigure 5 in Supplement 3). Placebo-corrected LDL-C levels changed at week 12 by −11.2% (95% CI, −25.3% to 5.5%), −16.0% (95% CI, −27.1% to −3.2%), and −21.3% (95% CI, −31.7% to −9.4%), respectively (eTable 3 in Supplement 3).

Safety and Tolerability

The percentages of participants reporting treatment-emergent adverse events were similar in all treatment groups (**Table 3**). Serious adverse events were reported in 6% or less of participants in each group and were single events spread across organ system classes. The incidence of adverse events leading to discontinuation of study drug varied from 0% to 9% across the treatment groups and involved single events

Table 3. Investigator-Reported Adverse Events and Abnormal Laboratory Findings[a]

Adverse events or laboratory findings	Muvalaplin 10 mg/d (n = 34)	Muvalaplin 60 mg/d (n = 63)	Muvalaplin 240 mg/d (n = 68)	Placebo (n = 67)
Adverse events, No. (%)				
Treatment-emergent adverse events	18 (52.9)	31 (49.2)	35 (51.5)	35 (52.2)
Treatment-emergent adverse events related to treatment	2 (5.9)	9 (14.3)	10 (14.7)	10 (14.9)
Serious adverse events	2 (5.9)	2 (3.2)	2 (2.9)	4 (6.0)
Adverse events leading to study treatment discontinuation	0	0	6 (8.8)	1 (1.5)
Deaths	0	0	0	0
Treatment-emergent adverse events occurring in ≥5% of participants in any group				
Nausea	2 (5.9)	1 (1.6)	0	3 (4.5)
Influenza	2 (5.9)	1 (1.6)	1 (1.5)	1 (1.5)
Back pain	2 (5.9)	0	0	2 (3.0)
Myalgia	2 (5.9)	1 (1.6)	1 (1.5)	0
Anemia	2 (5.9)	0	0	0
Diarrhea	0	1 (1.6)	4 (5.9)	4 (6.0)
Uterine leiomyoma[b]	0 [n = 11]	0 [n = 22]	0 [n = 24]	1 (5.3) [n = 19]
Laboratory findings				
Total bilirubin >2× upper limit of normal, No. (%)	0	0 [n = 62]	0	0
AST >3× upper limit of normal, No. (%)	0	0 [n = 62]	1 (1.5)	0
ALT >3× upper limit of normal, No. (%)	0	2 (3.2) [n = 62]	1 (1.5)	1 (1.5)
Plasminogen activity, least-squares mean % (95% CI)				
Baseline	102.9 (95.4 to 110.4)	98.8 (93.5 to 104.2) [n = 62]	98.3 (93.2 to 103.4)	97.5 (92.4 to 102.6) [n = 66]
Week 12	97.3 (93.0 to 101.5) [n = 29]	99.5 (96.2 to 102.7) [n = 53]	99.6 (96.5 to 102.7) [n = 57]	101.7 (98.5 to 104.9) [n = 56]
Absolute change	−1.5 (−5.7 to 2.8)	0.7 (−2.5 to 4.0)	0.9 (−2.2 to 4.0)	3.0 (−0.3 to 6.2)
% Change	−1.5 (−5.7 to 2.9)	0.7 (−2.5 to 4.1)	0.9 (−2.2 to 4.1)	3.0 (−0.2 to 6.3)
Placebo-adjusted % change	−4.4 (−9.3 to 0.9)	−2.2 (−6.5 to 2.2)	−2.1 (−6.2 to 2.3)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] Participants may be counted in more than 1 category. A treatment-emergent adverse event was defined as an event that first occurred or worsened in severity after first dose of study treatment. For participants who discontinued, the reason was collected, including for adverse events. Serious adverse events included the following: in the placebo group, 1 concussion while riding a go-kart, 1 peripheral arterial occlusive disease, 1 peripheral vascular hematoma following a fall in a patient treated with warfarin, and 1 wrist fracture following a fall from a standing height; in the 10-mg/d muvalaplin group, 1 bursitis and 1 lower limb fracture following a fall while riding a bike; in the 60-mg/d muvalaplin group, 1 atrial fibrillation and 1 dizziness and syncope (thought to be vasovagal); and in the 240-mg/d muvalaplin group, 1 incisional hernia and 1 priapism. Adverse events leading to study treatment discontinuation included 1 decreased glomerular filtration rate in the placebo group and 1 each of constipation, diarrhea, priapism, hypertransaminasemia, lethargy, and psoriasis in the 240-mg/d muvalaplin group.

[b] Denominators are female participants.

spread across organ system classes. Treatment-emergent adverse events occurring in at least 5% of participants in any group included diarrhea, nausea, influenza, back pain, myalgia, uterine leiomyoma, and anemia. Hepatic safety was similar across the groups, and no participants had elevation of both liver enzymes and bilirubin. One participant with a history of metabolic dysfunction-associated steatohepatitis and elevated baseline alanine aminotransferase treated with 240 mg/d of muvalaplin demonstrated aspartate aminotransferase and alanine aminotransferase concentrations greater than 10 times the upper limit of normal at 1 visit, with no elevation of bilirubin. This occurred while the participant was being treated with penicillin for a tooth infection and subsequently resolved. There was no significant change in plasminogen levels at week 12 with muvalaplin (Table 3). One patient in the placebo group underwent a peripheral artery percutaneous revascularization.

Discussion

This phase 2 study demonstrated that muvalaplin, an oral agent that inhibits lipoprotein(a) formation, was well tolerated and reduced lipoprotein(a) levels. At the highest dose studied, 240 mg, muvalaplin produced a placebo-adjusted reduction of intact lipoprotein(a) of 85.8% and a reduction of lipoprotein(a) as measured by a traditional apolipoprotein(a)-based assay of 68.9%. The 240-mg/d dosage resulted in 96.7% of patients achieving lipoprotein(a) concentrations of less than 125 nmol/L using an intact lipoprotein(a) assay and 77.4% using

an apolipoprotein(a) assay. Dose-dependent reductions in LDL-C and apolipoprotein B of up to 21.3% and 16.1%, respectively, were also observed. Muvalaplin was well tolerated, with no dose-dependent adverse events and no concerning biochemical abnormalities.

Muvalaplin is the first oral small molecule inhibitor that reduces lipoprotein(a) levels. Production of lipoprotein(a) comprises a 2-step process involving noncovalent binding of apolipoprotein(a) kringle IV domains 7 and 8 to lysine residues of apolipoprotein B, followed by formation of a covalent disulfide bond.[17] Muvalaplin binds to apolipoprotein(a) kringle IV domains 7 and 8, disrupting the initial noncovalent interaction between apolipoprotein(a) and apolipoprotein B, preventing the formation of lipoprotein(a) particles.[17] This mechanism mimics naturally occurring apolipoprotein(a) variants that cannot interact with apolipoprotein B and result in low lipoprotein(a) levels.[24,25] Preclinical studies confirmed that muvalaplin inhibited in vitro lipoprotein(a) assembly and reduced lipoprotein(a) levels in nonhuman primates.[17] Administration of muvalaplin for 14 days in a phase 1 study demonstrated good tolerability with dose-dependent lipoprotein(a) lowering.[18] The current findings demonstrate lipoprotein(a) lowering with muvalaplin over a longer period and in a larger cohort of patients with elevated lipoprotein(a) levels who are at high risk of cardiovascular events.

The present study prespecified measuring lipoprotein(a) using both a traditional apolipoprotein(a)-based assay and an intact lipoprotein(a) assay. Because commercially available lipoprotein(a) assays measure apolipoprotein(a) bound to apolipoprotein B in intact lipoprotein(a) particles, in addition to apolipoprotein(a) bound to muvalaplin and free apolipoprotein(a), they have the potential to underestimate the degree of lipoprotein(a) lowering with agents like muvalaplin. The novel intact lipoprotein(a) assay was used to measure the concentration of lipoprotein(a) particles by detecting only apolipoprotein(a) that is part of an apolipoprotein B-containing particle. Consistent with its mechanism, muvalaplin produced greater dose-dependent reductions in intact lipoprotein(a) than in lipoprotein(a) measured with a traditional apolipoprotein(a)-based assay.[26,27] Muvalaplin also produced dose-dependent lowering of oxidized phospholipid concentrations. Oxidized phospholipids carried on lipoprotein(a) particles are thought to contribute to their pathogenicity in atherosclerosis[28] and calcific aortic valve stenosis[7] via promotion of inflammation.

Considerable sequence homology is present between apolipoprotein(a) and plasminogen.[29] Lipoprotein(a) can competitively inhibit plasminogen activity, likely contributing to its prothrombotic effects. Given this, the impact of lipoprotein(a)-lowering therapies on plasminogen activity is of considerable interest. The current findings confirm the earlier reports from the phase 1 study that muvalaplin had no discernible effect on plasminogen activity.[17,18]

Limitations

This study has several limitations. First, this study evaluated the effect of treatment with muvalaplin for 12 weeks; the impact of longer administration on efficacy and safety requires further evaluation. Second, the intact lipoprotein(a) assay is not available in clinical practice and has not yet been widely evaluated. Third, it is unknown if apolipoprotein(a) bound to muvalaplin has any biological effects. There is currently no evidence that this complex can transport cholesterol and oxidized phospholipids. Therefore, apolipoprotein(a) bound to muvalaplin may simply be a transient complex without biological activity. Fourth, the primary efficacy end point was analyzed excluding observations after patients discontinued study drug or initiated lipoprotein(a)-modifying medication. When analyzed under a modified intention-to-treat framework, the degree of lipoprotein(a) lowering at week 12 was similar. Fifth, whether lipoprotein(a) lowering reduces cardiovascular risk and the degree of lowering required to produce meaningful benefit remains uncertain.

Conclusions

While most therapies in clinical development have used injectable agents that target apolipoprotein(a) messenger RNA, muvalaplin inhibits lipoprotein(a) assembly with oral delivery, with evidence of effective lipoprotein(a) lowering and a favorable safety and tolerability profile. Future studies are needed to determine whether muvalaplin reduces clinical events and plays a role in the prevention of cardiovascular disease.

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