Original Investigation

Effect of Losmapimod on Cardiovascular Outcomes in Patients Hospitalized With Acute Myocardial Infarction
A Randomized Clinical Trial

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IMPORTANCE p38 Mitogen-activated protein kinase (MAPK)–stimulated inflammation is implicated in atherogenesis, plaque destabilization, and maladaptive processes in myocardial infarction (MI). Pilot data in a phase 2 trial in non–ST elevation MI indicated that the p38 MAPK inhibitor losmapimod attenuates inflammation and may improve outcomes.

OBJECTIVE To evaluate the efficacy and safety of losmapimod on cardiovascular outcomes in patients hospitalized with an acute myocardial infarction.

DESIGN, SETTING, AND PATIENTS LATITUDE-TIMI 60, a randomized, placebo-controlled, double-blind, parallel-group trial conducted at 322 sites in 34 countries from June 3, 2014, until December 8, 2015. Part A consisted of a leading cohort (n = 3503) to provide an initial assessment of safety and exploratory efficacy before considering progression to part B (approximately 22 000 patients). Patients were considered potentially eligible for enrollment if they had been hospitalized with an acute MI and had at least 1 additional predictor of cardiovascular risk.

INTERVENTIONS Patients were randomized to either twice-daily losmapimod (7.5 mg; n = 1738) or matching placebo (n = 1765) on a background of guideline-recommended therapy. Patients were treated for 12 weeks and followed up for an additional 12 weeks.

MAIN OUTCOMES AND MEASURES The primary end point was the composite of cardiovascular death, MI, or severe recurrent ischemia requiring urgent coronary revascularization with the principal analysis specified at week 12.

RESULTS In part A, among the 3503 patients randomized (median age, 66 years; 1036 [29.6%] were women), 99.1% had complete ascertainment for the primary outcome. The primary end point occurred by 12 weeks in 123 patients treated with placebo (7.0%) and 139 patients treated with losmapimod (8.1%; hazard ratio, 1.16; 95% CI, 0.91-1.47; *P* = .24). The on-treatment rates of serious adverse events were 16.0% with losmapimod and 14.2% with placebo.

CONCLUSIONS AND RELEVANCE Among patients with acute MI, use of losmapimod compared with placebo did not reduce the risk of major ischemic cardiovascular events. The results of this exploratory efficacy study did not justify proceeding to a larger efficacy trial in the existing patient population.

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The p38 mitogen-activated protein kinase (MAPK) is an intracellular kinase that is expressed in multiple cells, including endothelial cells, myocytes, and macrophages,[1] and participates in numerous adaptive and maladaptive biological processes, including inflammation, as well as cellular migration, growth, and death.[2] The enzyme is activated in the cardiovascular system by a variety of stressors, including oxidized low-density lipoprotein cholesterol, hypertension, ischemia, and volume overload.[1,3] Activation of p38 MAPK leads to amplification of the inflammatory cascade through enhanced production of multiple cytokines, including tumor necrosis factor, interleukins 1 and 6, metalloproteinases, and cyclooxygenase 2.[4] MAPK-mediated inflammatory amplification has been implicated in atherogenesis, plaque destabilization, and detrimental processes in infarction and wound healing.[2,5]

hs-CRP *high-sensitivity C-reactive protein*

MAPK *p38 mitogen-activated protein kinase*

NT-pro-BNP *N-terminal pro–brain natriuretic peptide*

Losmapimod is a selective, reversible, competitive inhibitor of p38 MAPK with onset as early as 30 minutes after oral dosing. In a randomized trial of 526 patients hospitalized with non–ST-elevation myocardial infarction (NSTEMI), losmapimod, administered prior to percutaneous coronary intervention (PCI), attenuated the acute increase in markers of inflammation (C-reactive protein and interleukin 6) at 72 hours. However, the effects were no longer significant at 12 weeks and the drug did not reduce periprocedural myonecrosis. Although the trial was not powered for clinical efficacy, the incidence of death, MI, recurrent ischemia, stroke, or heart failure was lower in patients treated with losmapimod, although the difference was not statistically significant (hazard ratio [HR], 0.82; 95% CI, 0.49-1.37).[6] Furthermore, in a subgroup of patients who underwent cardiac magnetic resonance imaging, losmapimod improved left ventricular function consistent with reduced adverse ventricular remodeling.

Therefore, we hypothesized that losmapimod may mitigate a number of complications that occur in patients with acute MI.[7] The Losmapimod to Inhibit p38 MAP Kinase as a Therapeutic Target and Modify Outcomes After an Acute Coronary Syndrome (LATITUDE)-TIMI 60 trial was a multinational phase 3 trial designed to test the efficacy and safety of the p38 MAPK inhibitor losmapimod when added to existing care for patients with acute MI, both NSTEMI and STEMI.

Methods

The study design has been described,[7] and the trial protocol is provided in Supplement 2. In brief, the trial was a randomized, placebo-controlled, double-blind, parallel-group, multinational trial that was planned to occur in 2 major parts. The trial was conducted at 322 sites in 34 countries (eAppendix in Supplement 1). In the first stage of the trial (part A), a leading cohort of patients was enrolled to provide an initial assessment of safety and exploratory efficacy before progressing to the main cohort (part B). Part B was to be event driven, with approximately 22 000 patients randomized in the main cohort to provide the primary assessment of the efficacy of losmapimod. By design, on completion of the treatment phase of part A, a selected group of individuals involved in the trial leadership from the TIMI Study Group and the sponsor reviewed unblinded summary data from part A and the decision was made that the data did not support proceeding to part B. This article reports the final results of part A. The decision to proceed to part B was planned to be multifaceted and based in part on the probability of demonstrating a statistically significant reduction in cardiovascular events in part B, given the totality of the observed data in part A.

The protocol was approved by the relevant institutional review boards or ethics committees, and all participants gave written informed consent.

Study Population

Patients were considered eligible for enrollment if they were aged 35 years or older; had been hospitalized with a presumed spontaneous (type 1) MI, including NSTEMI within 24 hours of ischemic symptoms or STEMI within 12 hours of onset; and had at least 1 additional predictor of cardiovascular risk.[7] Study drug was to be administered as early as possible during hospitalization and prior to coronary revascularization or reperfusion. Relevant exclusion criteria at study entry included clinical instability, known acute or chronic liver disease, current life-threatening or opportunistic infection, severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2), or New York Heart Association class III or IV or Killip class III or IV heart failure at randomization.

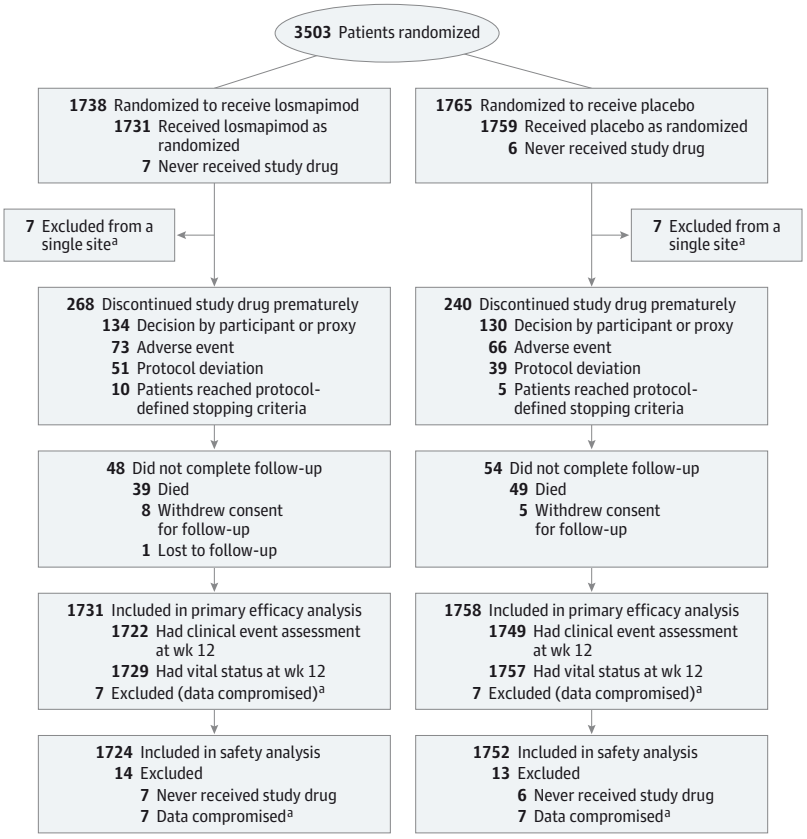
Study Procedures

After providing informed consent, eligible patients were randomly assigned at the site level in a 1:1 ratio, stratified by the qualifying type of MI (NSTEMI or STEMI), through a central computerized system to receive either losmapimod (7.5 mg orally twice daily) or matching placebo for 12 weeks (**Figure 1**). Each patient was then to be followed up for an additional 12 weeks, for a total study participation of 24 weeks. Any patient who discontinued study drug prematurely was still followed up for outcomes and included in efficacy analyses according to the intention-to-treat principle. Close adherence to local professional society guidelines for standard-of-care therapies in acute coronary syndrome was emphasized throughout study conduct. Patient race was self-reported and captured in the electronic case-report form by site personnel to assess homogeneity of drug response.

End Points

The primary end point was major adverse cardiovascular events, defined as the composite of cardiovascular death, MI, or severe recurrent ischemia requiring urgent coronary artery revascularization. The principal secondary end point was the composite of cardiovascular death or MI. Additional cardiovascular outcomes of heart failure, stroke, and unplanned coronary revascularization were also assessed. A complete list of secondary outcomes is included in the eTable in Supplement 1.[7]

Figure 1. Participant Flow in the LATITUDE-TIMI 60 Trial



Database did not include the number of individuals screened for study participation or the number excluded before randomization.

[a] Compromise of data integrity at a single site led to exclusion of data in 14 participants.

An independent and blinded clinical events committee that was designed and implemented by the TIMI Study Group adjudicated all reported deaths, cardiac ischemic events, cerebrovascular events, stent thrombosis, and hospitalizations for heart failure according to prespecified definitions.[7]

Biomarkers

As a prespecified exploratory analysis, high-sensitivity C-reactive protein (hs-CRP; Olympus Latex) was to be measured in all participants at randomization, week 4, week 12, and week 24. In addition, in a subset of participants, serial assessment was also performed for hs-CRP (n = 631) at 48 hours, week 13, and week 18 and N-terminal pro-brain natriuretic peptide (NT-pro-BNP; n = 1199; Roche Diagnostics) at week 4, week 12, and week 24.

Statistical Analysis

It was anticipated that approximately 3500 patients in part A would yield approximately 200 to 250 primary end points to be used to judge whether to continue to part B, the design of which has been detailed previously.[7] The sample size for part A was in part determined using simulation techniques to model the number of events at which the volatility in the effect estimate converged with modest subsequent gain. A sample size of 3500 participants was needed to accrue the target number of primary end points, based on a projected 12-week event rate of 7.0% in the placebo group and a 16% relative risk reduction in the losmapimod group.

As outlined in the reporting and analysis plan (Supplement 2), efficacy analyses included all randomized participants, with the exception of patients at a single site where data integrity was compromised, leading to their exclusion from all efficacy and safety analyses (n = 14 patients). Sensitivity analyses were performed including these 14 participants without any meaningful change in the results. Safety analyses were conducted among patients who received at least 1 dose of study drug. The primary analysis was time to event using a log-rank test stratified by the type of qualifying MI (NSTEMI vs STEMI). Cumulative event rates were calculated using the Kaplan-Meier method at 12 weeks (day 84) for the primary analyses and then through full follow-up through 24 weeks. Estimated HRs and 95% confidence intervals were obtained using a Cox proportional hazards regression model with the same stratification factor. The Cox proportional hazards assumption was reviewed and deemed to be met. Analyses were assessed using a 2-sided significance threshold of $P<.05$, including secondary end points and subgroup interactions. All analyses of secondary end points and interactions should be interpreted as exploratory. All statistical analyses were performed with SAS version 9.3 (SAS Institute Inc) and R software (http://www.r-project.org).

Table 1. Baseline Characteristics of the Study Population by Randomized Treatment Group[a]

Characteristics	Losmapimod (n = 1731)	Placebo (n = 1758)
Demographics		
Age, median (IQR), y	66 (61-74)	67 (61-73)
≥60	1376 (79.5)	1394 (79.3)
Female	500 (28.9)	532 (30.3)
Body mass index, median (IQR)[b]	28 (25-31)	28 (25-31)
Race		
White	1585 (91.6)	1616 (92.1)
Black	20 (1.2)	25 (1.4)
Asian	105 (6.1)	99 (5.6)
Other	21 (1.2)	15 (0.9)
Region		
North America	236 (13.6)	233 (13.3)
Eastern Europe	687 (39.7)	703 (40.0)
Western Europe	580 (33.5)	590 (33.6)
South America	42 (2.4)	45 (2.6)
Asia-Pacific	186 (10.7)	187 (10.6)
Medical history		
Hypertension	1268 (73.3)	1276 (72.6)
Hyperlipidemia	985 (56.9)	936 (53.2)
Diabetes mellitus	582 (33.6)	586 (33.3)
Current smoker	464 (26.8)	449 (25.6)
Prior myocardial infarction	425 (24.6)	426 (24.2)
Prior PCI	412 (23.8)	410 (23.3)
Baseline eGFR ≤60 mL/min/1.73 m^2[c]	258 (15.8)	265 (16.1)
Prior heart failure	206 (11.9)	216 (12.3)
Prior coronary artery bypass graft surgery	154 (8.9)	137 (7.8)
Prior peripheral arterial disease	109 (6.4)	115 (6.6)
Prior ischemic stroke	90 (5.2)	105 (6.0)
Baseline laboratory values, median (IQR)[d]		
High-sensitivity C-reactive protein, mg/L	3.60 (1.70-9.60)	3.70 (1.70-9.90)
N-terminal pro-brain natriuretic peptide, pg/mL	391.2 (132.7-1416.0)	465.1 (153.7-1324.7)
Index events		
Qualifying myocardial infarction		
Non-ST-elevation myocardial infarction	1299 (75.0)	1325 (75.4)
ST-elevation myocardial infarction	432 (25.0)	433 (24.6)
Catheterization performed for qualifying event		
Non-ST-elevation myocardial infarction	1229 (94.6)	1261 (95.2)
ST-elevation myocardial infarction	421 (97.5)	424 (97.9)
PCI performed for qualifying event		
Non-ST-elevation myocardial infarction	814 (62.7)	807 (60.9)
ST-elevation myocardial infarction	387 (89.6)	397 (91.7)
Fibrinolytic for qualifying event	17 (1.0)	16 (0.9)
Time from study drug administration to coronary revascularization, median (IQR), h		
Non-ST-elevation myocardial infarction	1.7 (0.6-8.9)	1.8 (0.5-9.1)
ST-elevation myocardial infarction	0.2 (0.1-0.6)	0.2 (0.0-0.6)
Use of medical therapy at hospital discharge		
Aspirin	1634 (95.2)	1653 (94.8)
P2Y12 inhibitor	1498 (87.2)	1506 (86.4)
Statin	1626 (94.7)	1657 (95.1)
β-Blocker	1436 (83.7)	1481 (85.0)
ACE inhibitor or angiotensin receptor blocker	1339 (78.0)	1376 (78.9)

Abbreviations: ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PCI, percutaneous coronary intervention.

[a] Data are expressed as No. (%) of participants unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Estimated glomerular filtration rate was assessed using the Modification of Diet in Renal Disease equation.

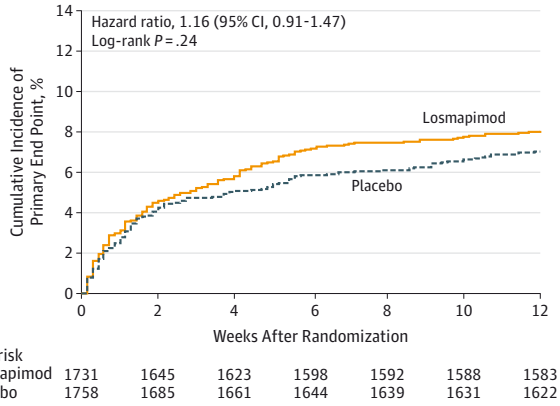
[d] Baseline high-sensitivity C-reactive protein data were available for 3306 participants; baseline N-terminal pro–brain natriuretic peptide data were available for 1199 participants.

Results

From June 3, 2014, until May 15, 2015, a total of 3503 participants were enrolled in part A of the trial. During the course of the study, a total of 3490 patients (99.6%) received at least 1 dose of study drug. Overall, 99.1% of participants had complete ascertainment for the primary outcome, and the final disposition of all study participants is summarized in Figure 1.

Baseline characteristics were well balanced between treatment groups (**Table 1**). The median age of enrolled participants was 66 years and 29.4% were women. The qualifying MI was a STEMI in 24.8%. The median time from symptom onset to randomization was 3.8 hours (interquartile range [IQR], 2.5-6.6 hours) for STEMI and 20.3 hours (IQR, 13.0-27.7 hours) for NSTEMI. For management of the qualifying event, 94.9% of patients with NSTEMI underwent cardiac catheterization and 61.8% underwent coronary revascularization. In patients with STEMI, 97.7% of patients underwent cardiac catheterization

Figure 2. Kaplan-Meier Curves for the Primary End Point



No. at risk

Losmapimod	1731	1645	1623	1598	1592	1588	1583
Placebo	1758	1685	1661	1644	1639	1631	1622

Cumulative incidence of the primary end point of cardiovascular death, myocardial infarction, or severe recurrent ischemia leading to urgent revascularization through 12 weeks with losmapimod vs placebo.

Table 2. Efficacy End Points by Randomized Treatment Group in LATITUDE-TIMI 60 at 12 Weeks After Randomization

End Points	No. (%)[a] Losmapimod (n = 1731)	Placebo (n = 1758)	Hazard Ratio (95% CI)
Primary end point			
Cardiovascular death, myocardial infarction, or severe recurrent ischemia leading to urgent revascularization	139 (8.1)	123 (7.0)	1.16 (0.91-1.47)
Cardiovascular death	36 (2.1)	44 (2.5)	0.83 (0.53-1.28)
Myocardial infarction (fatal and nonfatal)	90 (5.3)	75 (4.3)	1.23 (0.91-1.67)
Severe recurrent ischemia leading to urgent revascularization	18 (1.1)	16 (0.9)	1.14 (0.58-2.24)
Secondary outcomes[b]			
Cardiovascular death or myocardial infarction	122 (7.1)	110 (6.3)	1.13 (0.88-1.47)
Cardiovascular death, myocardial infarction, or hospitalization for heart failure	140 (8.1)	131 (7.5)	1.09 (0.86-1.38)
Hospitalization for heart failure	35 (2.0)	42 (2.4)	0.84 (0.54-1.32)
Cardiovascular death, myocardial infarction, severe recurrent ischemia leading to urgent revascularization, or stroke	151 (8.8)	135 (7.7)	1.14 (0.91-1.44)
Stroke	14 (0.8)	15 (0.9)	0.95 (0.46-1.96)
Coronary heart disease death, myocardial infarction, severe recurrent ischemia leading to urgent revascularization, or any unplanned coronary revascularization	152 (8.8)	144 (8.2)	1.08 (0.86-1.36)
Cardiovascular death or hospitalization for heart failure	64 (3.7)	72 (4.1)	0.90 (0.64-1.26)
Cardiovascular death, myocardial infarction, or stroke	134 (7.8)	122 (7.0)	1.12 (0.88-1.43)
Cardiovascular death, myocardial infarction, severe recurrent ischemia leading to urgent revascularization, stroke, or hospitalization for heart failure	169 (9.8)	155 (8.8)	1.11 (0.90-1.39)
Definite or probable stent thrombosis[c]	11 (0.9)	19 (1.5)	0.57 (0.27-1.19)

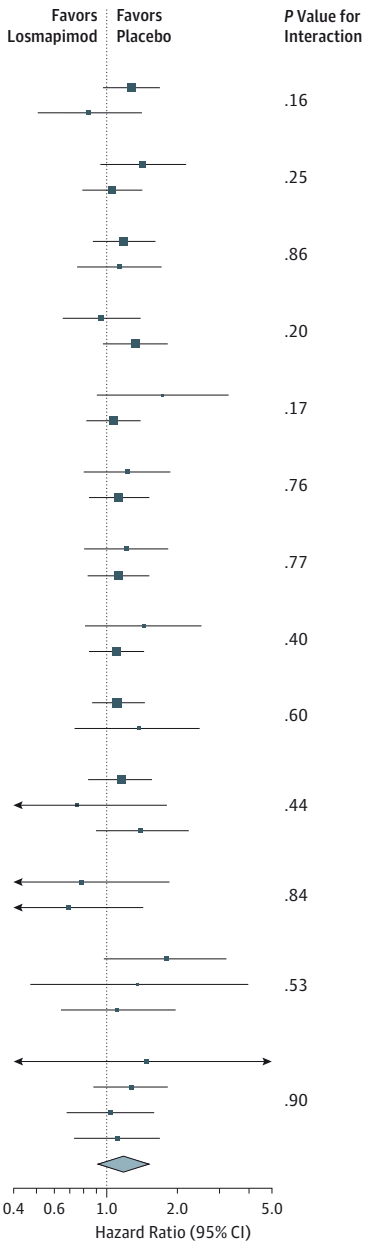
[a] Percentages are cumulative Kaplan-Meier event rates at 12 weeks. Kaplan-Meier rates and hazard ratios (all outcomes) are for the first occurrence of the event.

[b] Additional secondary outcomes included the substitution of coronary heart disease death for each of the composite outcomes that included cardiovascular death, as well as any rehospitalization at 30 days. The substitution did not qualitatively change any results and a neutral effect was observed for the odds of rehospitalization at 30 days.

[c] Denominator restricted to patients with a stent (n = 1306 for losmapimod and n = 1281 for placebo).

Figure 3. Hazard Ratios for the Primary End Point in Prespecified Subgroups of Interest at 12 Weeks After Randomization

Subgroup	Total No.		Events, No.		12-wk Kaplan-Meier Rate, %		Hazard Ratio (95% CI)	*P* Value for Interaction
	Losmapimod	Placebo	Losmapimod	Placebo	Losmapimod	Placebo		
Qualifying diagnosis								
Non-ST-elevation MI	1299	1325	111	90	8.6	6.8	1.27 (0.96-1.68)	.16
ST-elevation MI	432	433	28	33	6.5	7.6	0.84 (0.51-1.40)	
Age, y								
<65	723	714	51	36	7.1	5.1	1.42 (0.93-2.18)	.25
≥65	1008	1044	88	87	8.8	8.4	1.05 (0.78-1.41)	
Sex								
Male	1231	1226	94	80	7.7	6.5	1.18 (0.87-1.59)	.86
Female	500	532	45	43	9.0	8.1	1.13 (0.74-1.71)	
Diabetes mellitus								
Yes	582	586	52	55	9.0	9.4	0.95 (0.65-1.39)	.20
No	1149	1172	87	68	7.6	5.8	1.32 (0.96-1.81)	
Chronic kidney disease								
Yes	121	123	25	15	20.7	12.2	1.73 (0.91-3.28)	.17
No	1609	1635	113	108	7.0	6.6	1.07 (0.82-1.39)	
Prior MI								
Yes	425	426	48	40	11.4	9.4	1.22 (0.80-1.85)	.76
No	1306	1332	91	83	7.0	6.2	1.12 (0.84-1.51)	
Prior PCI or CABG surgery								
Yes	466	464	50	42	10.8	9.1	1.21 (0.80-1.82)	.77
No	1264	1294	88	81	7.0	6.3	1.12 (0.83-1.51)	
Prior heart failure								
Yes	206	216	28	21	13.6	9.8	1.43 (0.81-2.52)	.40
No	1524	1542	110	102	7.2	6.6	1.10 (0.84-1.44)	
Planned treatment strategy								
Invasive	1575	1603	115	105	7.3	6.6	1.12 (0.86-1.46)	.60
Conservative	156	155	24	18	15.4	11.6	1.34 (0.73-2.48)	
Actual treatment strategy								
PCI	1186	1189	87	78	7.4	6.6	1.13 (0.83-1.53)	
CABG surgery	152	155	9	12	5.9	7.8	0.75 (0.32-1.78)	.44
Medical management only	393	414	43	33	11.0	8.0	1.40 (0.89-2.20)	
Time from randomization to PCI (ST-elevation MI), min								
<30	217	221	9	12	4.2	5.5	0.76 (0.32-1.81)	.84
≥30	163	169	12	18	7.4	10.7	0.68 (0.33-1.41)	
Time from randomization to PCI (non-ST-elevation MI), h								
<3	425	419	30	17	7.1	4.1	1.77 (0.98-3.21)	.53
3 to <6	106	108	8	6	7.5	5.6	1.36 (0.47-3.93)	
≥6	209	218	25	24	12.0	11.0	1.11 (0.63-1.93)	
No. of predictors of cardiovascular risk								
0	40	40	3	2	7.5	5.0	1.51 (0.25-9.02)	.90
1	912	900	59	46	6.5	5.1	1.27 (0.87-1.87)	
2	466	518	36	39	7.8	7.6	1.03 (0.66-1.62)	
≥3	313	300	41	36	13.2	12.1	1.11 (0.71-1.73)	
Overall	1731	1758	139	123	8.1	7.0	1.16 (0.91-1.47)	



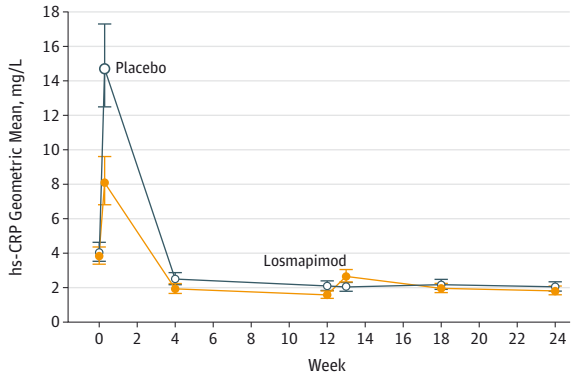
Hazard ratios for the primary end point (cardiovascular death, myocardial infarction [MI], or severe recurrent ischemia leading to urgent revascularization) with losmapimod vs placebo in various subgroups at 12 weeks. Predictors of cardiovascular risk included age 60 years or older, prior MI, prior coronary artery bypass graft (CABG) surgery, non–ST elevation with ST-segment depression, diabetes mellitus requiring pharmacotherapy or coexistent arterial disease in at least 1 other peripheral territory. PCI indicates percutaneous coronary intervention. Data marker sizes are weighted based on number of individuals in each subgroup.

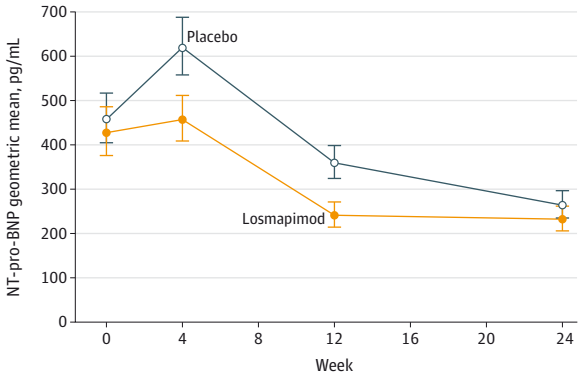
and 90.6% underwent coronary revascularization. Study drug was administered a median 0.2 hours (IQR, 0.1-0.6 hours) prior to primary PCI for patients with STEMI and 1.7 hours (IQR, 0.5-8.9 hours) prior to PCI for patients with NSTEMI.

Efficacy

Through week 12, the primary end point of cardiovascular death, MI, or severe recurrent ischemia leading to urgent revascularization occurred in 139 of 1731 patients (8.1%) allocated to losmapimod and 123 of 1758 patients (7.0%) allocated to placebo (HR, 1.16; 95% CI, 0.91-1.47; $P = .24$) (**Figure 2**). Because there was no evidence for efficacy for the primary outcome, all additional analyses are considered exploratory. The rates of the key secondary end point of cardiovascular death or MI were not significantly different between the 2 groups (HR, 1.13; 95% CI, 0.88-1.47) (**Table 2**). Each of the other secondary

Figure 4. Serial Biomarker Concentrations





Concentration of high-sensitivity C-reactive protein (hs-CRP) and N-terminal pro–brain natriuretic peptide (NT-pro-BNP) over time with losmapimod vs placebo. The errors bars indicate the 95% confidence interval around the geometric mean. For hs-CRP, *P*<.001 for losmapimod vs placebo at 48 hours and at week 12; *P*=.004 at week 4. For NT-pro-BNP, *P*<.001 for losmapimod vs placebo at week 4 and at week 12.

end points is reported in Table 2 and did not reveal any effect of losmapimod. Results were similar at week 24 in the overall cohort, with the primary end point having occurred in 10.3% of patients allocated to losmapimod and 9.7% allocated to placebo (HR, 1.11; 95% CI, 0.9-1.38).

Exploratory analyses of the effect of losmapimod were performed in prespecified subgroups. There was no statistically significant heterogeneity at 12 weeks for the primary outcome of cardiovascular death, MI, or severe recurrent ischemia leading to urgent revascularization within any of the prespecified subgroups (**Figure 3**).

Biomarkers

Biomarker concentrations were assessed as a prespecified exploratory outcome. Losmapimod reduced levels of the inflammatory biomarker hs-CRP at 4 weeks (ratio of the mean for losmapimod compared with placebo, 0.76; 95% CI, 0.62-0.91; *P*=.004 based on the geometric least square means) and at the end of the treatment period at 12 weeks (ratio of means, 0.73; 95% CI, 0.61-0.87; *P* < .001). In a planned subset of patients with testing at 48 hours after the initial dose during the index hospitalization, losmapimod attenuated the acute in-hospital increase in hs-CRP (**Figure 4**). N-terminal pro-BNP concentration was also significantly reduced at 4 weeks and 12 weeks in patients treated with losmapimod compared with placebo (Figure 4).

Safety

The incidence of any on-treatment serious adverse event was 16.0% for patients treated with losmapimod and 14.2% for patients treated with placebo (**Table 3**). Study drug was prematurely permanently discontinued in 15.5% of patients randomized to losmapimod and 13.7% of patients randomized to placebo. The incidence of any adverse event leading to permanent premature drug discontinuation was 4.4% in the losmapimod group and 3.9% in the placebo group. The incidence of liver enzyme abnormalities was similar by treatment group, although a trend toward a higher incidence of mildly elevated hepatic transaminases (>3 times the upper limit of normal) was observed for patients treated with losmapimod. The incidence of infections, including serious infections, was similar between treatment groups (Table 3).

Table 3. Incidence of Serious Adverse Events and Events of Special Interest by Treatment Group Through 24 Weeks After Randomization[a]

Events	Losmapimod (n = 1724)	Placebo (n = 1752)
Treatment duration, median (IQR), d[b]	88 (85-93)	88 (85-93)
Adverse events		
Any on-treatment serious adverse event, No. (%)	276 (16.0)	249 (14.2)
Any on-treatment adverse event leading to study drug discontinuation, No. (%)	75 (4.4)	69 (3.9)
Alanine aminotransferase measurements, No. (%)		
≥3× upper limit of normal (central laboratory)	29 (1.8)	22 (1.3)
≥5× upper limit of normal (central laboratory)	17 (1.1)	9 (0.5)
≥8× upper limit of normal (central laboratory)	11 (0.7)	8 (0.5)
≥3× upper limit of normal plus total bilirubin >2× upper limit of normal	5 (0.3)	4 (0.2)
Infection, No. (%)		
Any	46 (2.7)	42 (2.4)
Opportunistic	6 (0.3)	7 (0.4)
Acute kidney failure, No. (%)	18 (1.0)	15 (0.9)

Abbreviation: IQR, interquartile range.

[a] Incidence rates are reported in the safety population (participants who took ≥1 dose of study drug).

[b] Calculated as the difference between start and stop dates.

Discussion

In this trial, losmapimod did not reduce the risk of recurrent major adverse cardiovascular events through 12 weeks of treatment in patients hospitalized with acute MI. Furthermore, there was no evidence that losmapimod reduced the incidence of any secondary outcomes including all-cause mortality. Therefore, our findings do not support a strategy of p38 MAPK inhibition with losmapimod in patients hospitalized with MI.

Prior to the current trial, both preclinical and early clinical evidence supported the concept that p38 MAPK inhibition could reduce the risk of recurrent cardiovascular events.[1,7] Specifically, p38 MAPK has been implicated in preclinical models to contribute to cardiac fibrosis and dysfunction in postinfarction remodeling and heart failure,[8,9] in addition to myocyte death during myocardial ischemia.[10,11] In patients enrolled in the phase 2 trial in MI, losmapimod significantly improved left ventricular ejection fraction, reduced left ventricular end-diastolic and end-systolic volume, and lowered NT-pro-BNP concentration at 12 weeks.[6] p38 MAPK inhibition has been shown to reduce vascular inflammation as assessed by cellular uptake of ^{18}F-fluorodeoxyglucose uptake on positron emission tomography–computed tomography, improve vascular function, and attenuate the periprocedural increase in C-reactive protein in patients undergoing elective or urgent PCI, with a numerically lower number of cardiovascular events that did not achieve statistical significance in a prior phase 2 trial.[6,12,13] In LATITUDE-TIMI 60, losmapimod reduced periprocedural levels of the inflammatory marker hs-CRP in a broad spectrum of patients with acute MI and significantly reduced NT-pro-BNP concentration; however, this did not translate into clinical benefit.

Because inflammation is believed to play a key role in atherogenesis, there remains intense interest to identify an anti-inflammatory therapeutic that will reduce the risk of cardiovascular events.[14,15] However, because inflammation acts along multiple redundant and interconnected pathways, the identification of an appropriate target may be difficult, and it is challenging to predict clinical efficacy prior to phase 3 testing.[16,17] As such, the current phase 3 trial incorporated a multistage design that allowed preliminary insight into drug efficacy prior to expansion into the full study cohort of more than 22 000 patients. By incorporating multiple stages into a single phase 3 trial, efficiency is streamlined; thus, this type of adaptive study design may potentially serve as a model for future trials. Ongoing clinical trials are currently evaluating additional anti-inflammatory therapeutics in patients with atherosclerosis and will provide further insight into pathways that contribute to vascular disease.[15]

Limitations to the current study warrant consideration. Part A was designed to provide an exploratory assessment of efficacy and was not designed with statistical power for individual end points. Nonetheless, given the observed effect estimates, the posterior probability of a meaningful effect of losmapimod in the broad population studied is extremely low. Specifically, given the observed result in part A, the probability of a treatment effect of 15% or more being observed in the overall MI population planned to be studied in part B was less than 1%. Given this primary result, any signals toward potential efficacy in subgroups should be considered only hypothesis generating. Only a single dosage of study drug was selected for study and, thus, one cannot preclude the possibility that alternate dosages would have led to differing results. However, surrogate pharmacodynamic data did not suggest greater anti-inflammatory effects at higher dosages and, therefore, the current dosage was selected on the perceived balance of potential efficacy and tolerability. As well, the treatment course was limited in duration and, therefore, the results do not address the efficacy of longer-term anti-inflammatory therapy.

Conclusions

Among patients with acute MI, use of losmapimod compared with placebo did not reduce the risk of major ischemic cardiovascular events. The results of this exploratory efficacy study did not justify proceeding to a larger efficacy trial in the existing patient population.

ARTICLE INFORMATION

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