LATITUDE-TIMI 60

Losm**A**pimod **T**o **I**nhibi**T** p38 MAP kinase as a therape**U**tic target and mo**D**ify outcomes after an acute coronary syndrom**E**

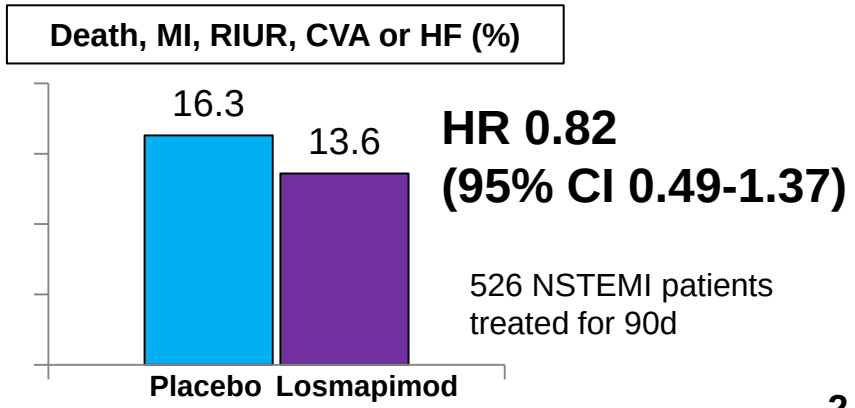
NCT02145468 (www.clinicaltrials.gov)

Michelle L. O'Donoghue, MD MPH
On behalf of the LATITUDE-TIMI 60 investigators

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Losmapimod Background

- **Anti-inflammatory agent that inhibits p38 mitogen-activated protein kinase (MAPK) dependent cytokine induction**
- **Preclinical: suppression of vascular inflammation; myocardial protection; attenuate reperfusion injury**
- **Phase II results in NSTEMI patients (SOLSTICE trial)***
  - Blunted rise in C-reactive protein (hsCRP)
  - ↓ B-type natriuretic peptide (BNP) and improved left ventricular function (exploratory) at 3 months
  - Trend toward lower risk of recurrent myocardial infarction
  - Favorable safety/tolerability



*Newby et al., *Lancet* 2014;384:1187

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2 Stage Design

A: Exploratory
N ~ 3500
~ 200 MACE events

B: Confirmatory Main
N ~ 22,000
~1400 MACE events (event driven)

Seamless transition (minimize gap)

Primary efficacy analysis would be based exclusively on Part B

Efficacy & Safety Assessment

- TIMI
- Sponsor
- Independent Data Monitoring Committee

O'Donoghue ML et al., *Am Heart J* 2015;169:622

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Study Design

Hospitalization w/ Myocardial Infarction
(NSTEMI ≤24h from last sx, STEMI ≤12h sx onset)

N=3,503
Part A

RANDOMIZE 1:1 (Stratified by NSTEMI/STEMI)
DOUBLE BLIND

Losmapimod 7.5 mg BID

PLACEBO

Study drug prior to any coronary revascularization or fibrinolysis for qualifying event

Study Treatment for *12 weeks*

End of Treatment Visit
(Primary Efficacy Evaluation)

Post-treatment F/U at 24 weeks

Anticipated
n~200 1º EP
(Part A)

1° EP: CV Death, MI, Severe Recurrent Ischemia → Urgent Revasc
Principal 2° EP: CV Death, MI

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Trial Organization

TIMI Study Group

Marc S. Sabatine (Study Chair)
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Stephen D. Wiviott (CEC Chair)
Laura Grip & Abby Cange (Operations)
Cheryl Lowe (CEC Director)
David A. Morrow (Global PI)
Matt Cavender & Tony Gutierrez (Co-Invs)
Marc P. Bonaca (Safety Chair)
Kelly Im & Julia Kuder (Statistics)

Executive Committee

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Philip Aylward
José López-Sendón
Pierre Theroux
David A. Morrow (Global PI)
Keith Fox
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Sponsor: GlaxoSmithKline

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Independent Data Monitoring Committee

Jeffrey L. Anderson (Chair)
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James A. de Lemos
Freek W. A. Verheugt

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BULGARIA (73)
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ESTONIA (99)
FRANCE (97)
Gabriel Steg
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GREECE (76)
Dimitrios Tziakas
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34 countries
322 sites 3503 subjects

Complete f/u was obtained in 99.4% of patients
Only 1 patient was lost to follow up

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Demographic and Baseline Characteristics

	Losmapimod (N=1731)	Placebo (N=1758)
Median Age (IQR)	66 (61-74)	67 (61-73)
Female (%)	29	30
White Race (%)	92	92
Median BMI (IQR)	28 (25-31)	28 (25-31)
Current Smoker (%)	27	26
History of Diabetes Mellitus (%)	34	33
Prior MI (%)	25	24
Prior Heart Failure (%)	12	12
Baseline eGFR ≤60ml/min/1.73m^2 (%)	16	16

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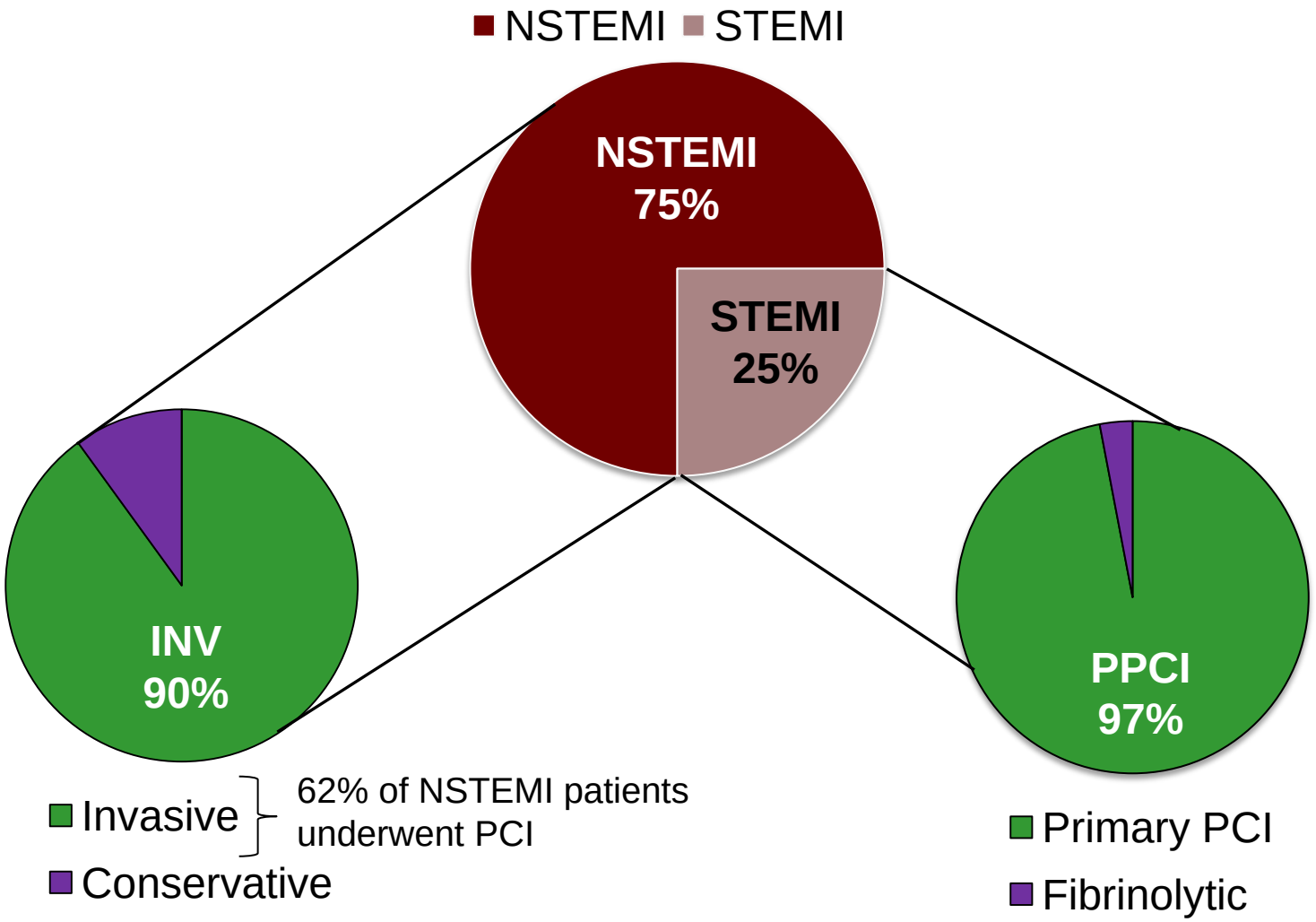
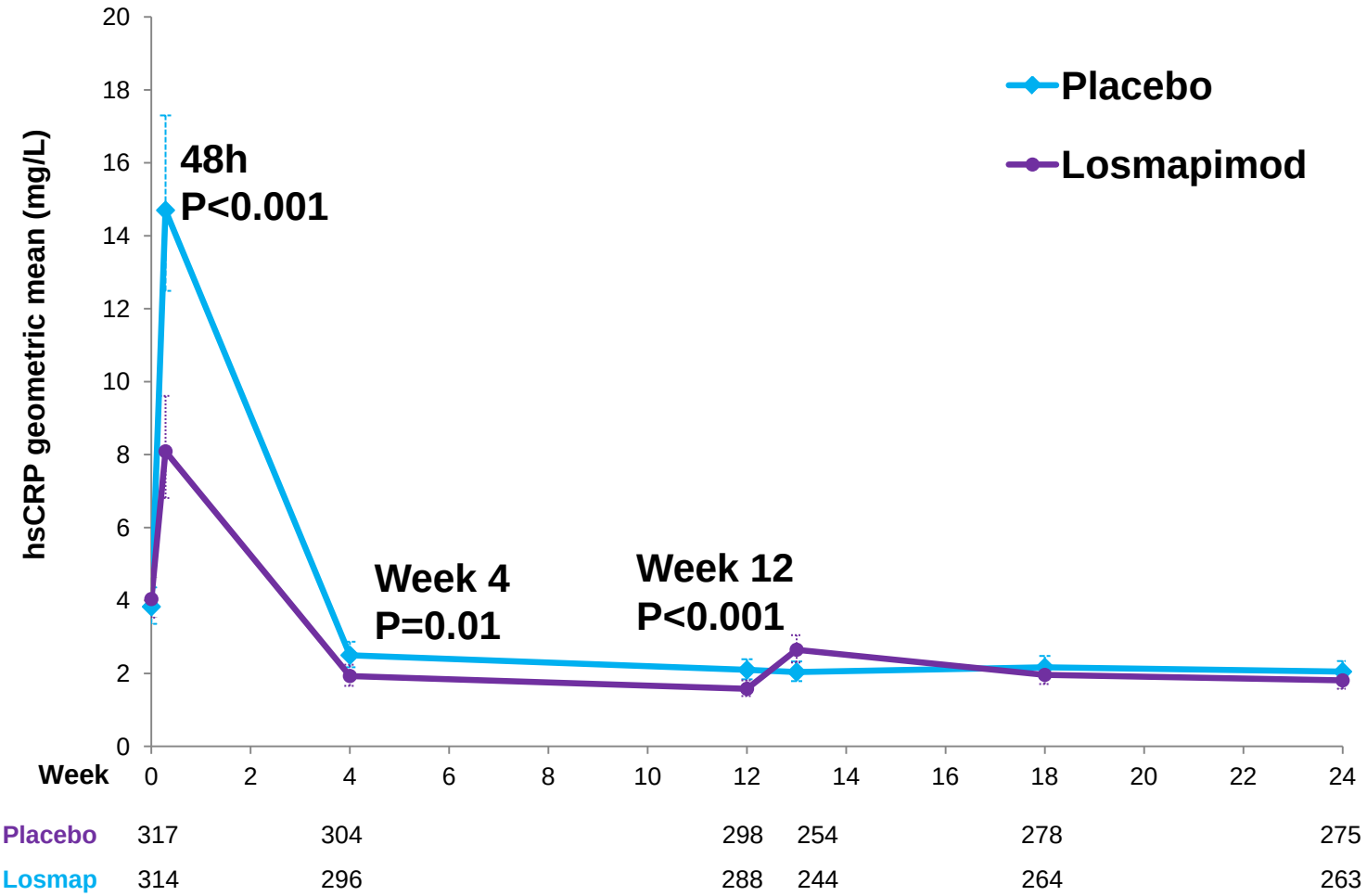
Details of Qualifying Event



Time From Study Drug Administration to Coronary Revascularization

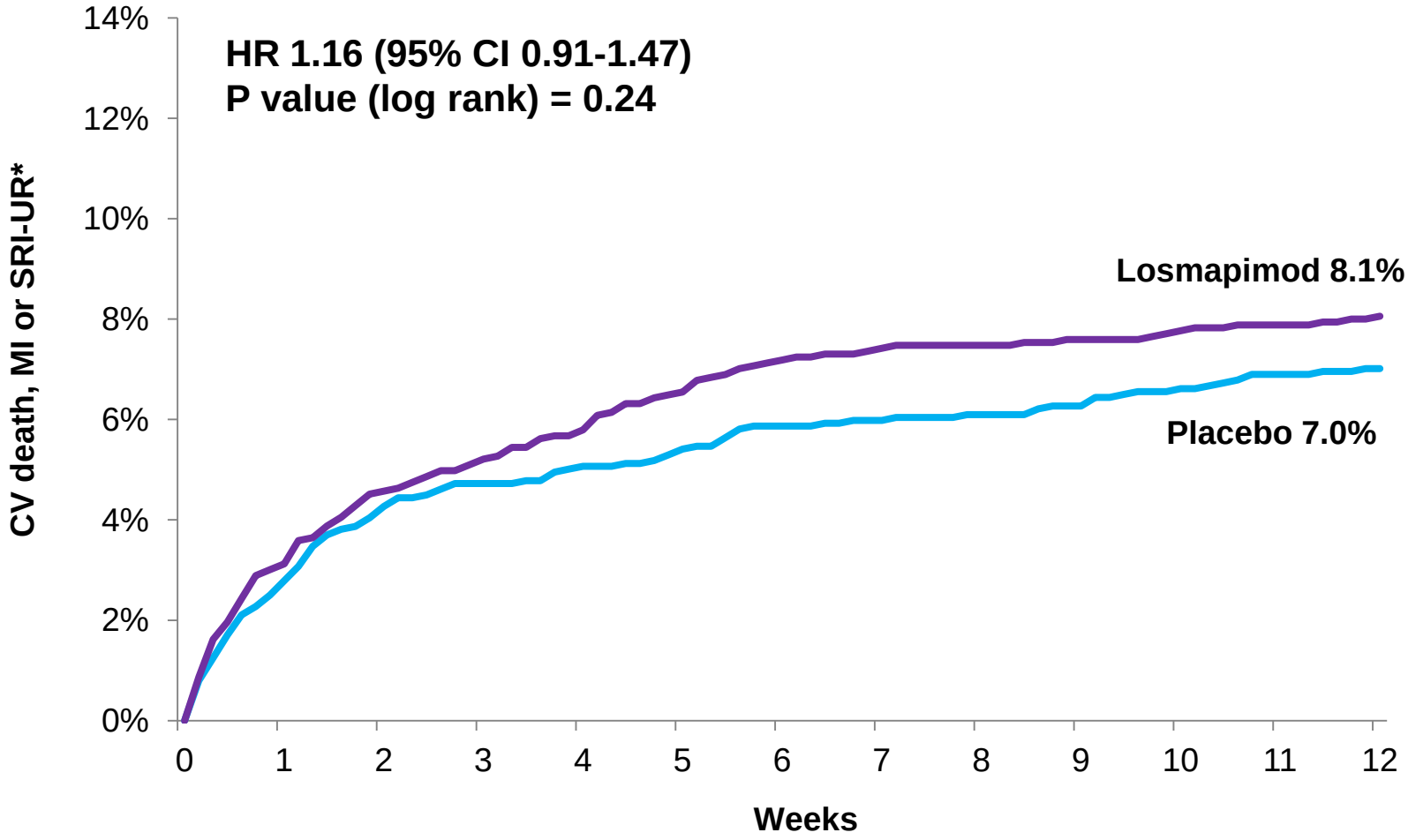
	Losmapimod	Placebo
NSTEMI (hours, median, IQR)	1.7 (0.6-8.9)	1.8 (0.5-9.1)
STEMI (hours, median, IQR)	0.2 (0.1-0.6)	0.2 (0.0-0.6)

Inflammatory Response after ACS (Serial C-reactive protein)



Error bars indicate 95% confidence intervals

Primary Endpoint (MACE) through Week 12



*SRI-UR: severe recurrent ischemia requiring urgent coronary revascularization

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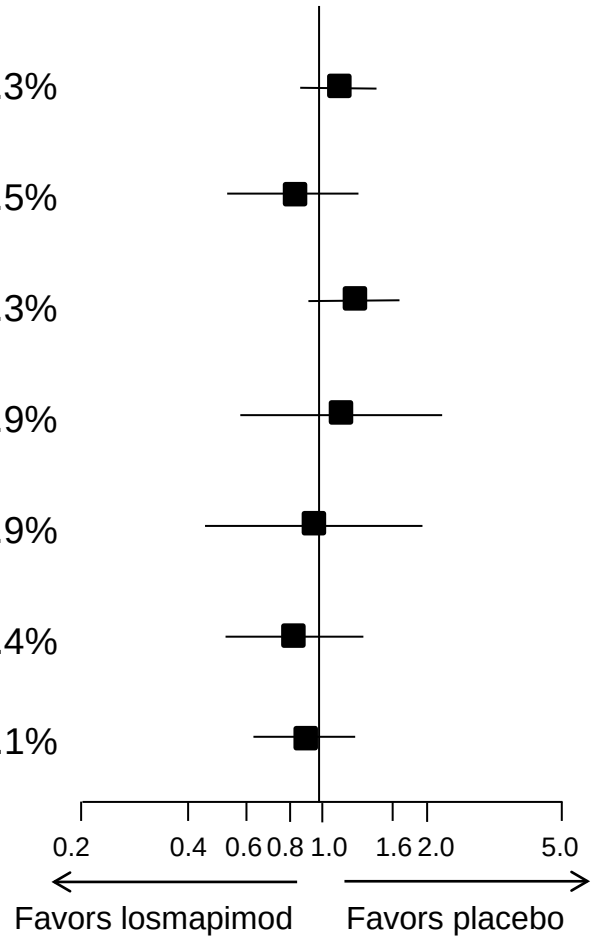
Secondary Outcomes

Outcome	12 week KM rate Losmapimod	Placebo	Hazard Ratio (95% CI)
CV death or MI	7.1%	6.3%	1.13 (0.88-1.47)
CV death	2.1%	2.5%	0.83 (0.53-1.28)
Fatal or non-fatal MI	5.3%	4.3%	1.23 (0.91-1.67)
SRI-UR*	1.1%	0.9%	1.14 (0.58-2.24)
Stroke	0.8%	0.9%	0.95 (0.46-1.96)
Hospitalization for HF	2.0%	2.4%	0.84 (0.54-1.32)
CV death or hosp for HF	3.7%	4.1%	0.90 (0.64-1.26)



*SRI-UR: severe recurrent ischemia requiring urgent coronary revascularization

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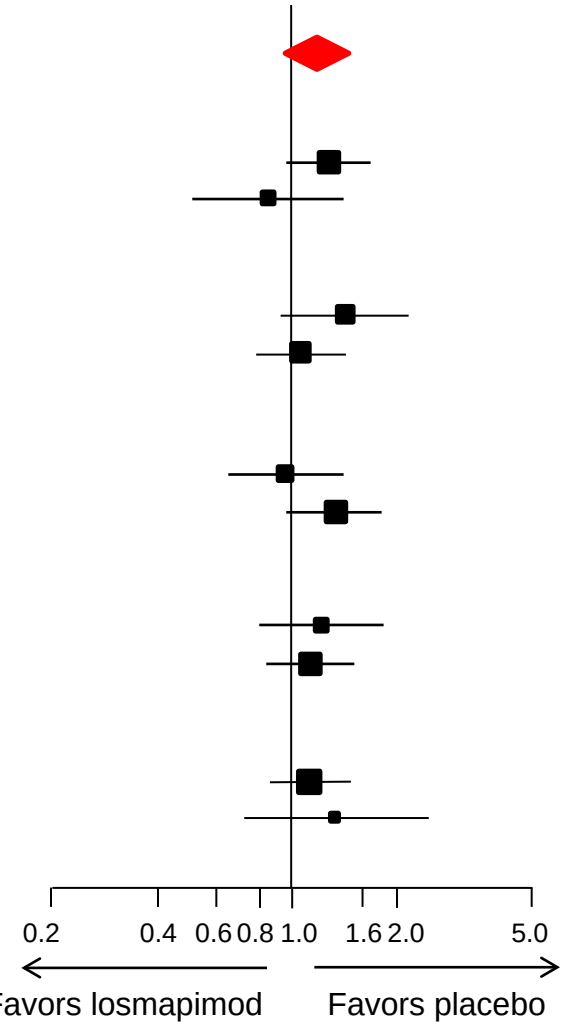
Safety

Adverse Events	Losmapimod (N=1724)	Placebo (N=1752)
Any on-treatment serious adverse event	276 (16.0%)	249 (14.2%)
Any on-treatment adverse event leading to study drug discontinuation	75 (4.4%)	69 (3.9%)
ALT ≥3x ULN	29 (1.8%)	22 (1.3%)
ALT ≥5x ULN	17 (1.1%)	9 (0.5%)
ALT ≥3x ULN and total bilirubin >2x ULN	5 (0.3%)	4 (0.2%)
Any infection	46 (2.7%)	42 (2.4%)

Abbreviation: ULN, upper limit normal

Subgroup Analyses: Primary Endpoint through Week 12

Subgroup	Total #	CVD death, MI or SRI-UR*	Hazard Ratio (95% CI)	P value for interaction
Overall	3489		1.16 (0.91-1.47)	
Qualifying diagnosis				
NSTEMI	2624		1.27 (0.96-1.68)	0.16
STEMI	865		0.84 (0.51-1.40)	
Age				
<65 years	1437		1.42 (0.93-2.18)	0.25
≥65 years	2052		1.05 (0.78-1.41)	
Diabetes mellitus				
Yes	1168		0.95 (0.65-1.39)	0.20
No	2321		1.32 (0.96-1.81)	
Prior MI				
Yes	851		1.22 (0.80-1.85)	0.76
No	2638		1.12 (0.84-1.51)	
Planned Rx strategy				
Invasive	3178		1.12 (0.86-1.46)	0.60
Conservative	311		1.34 (0.73-2.48)	



*SRI-UR: severe recurrent ischemia requiring urgent coronary revascularization

Serial hsCRP in NSTEMI & STEMI Cardiac Biomarker Substudy

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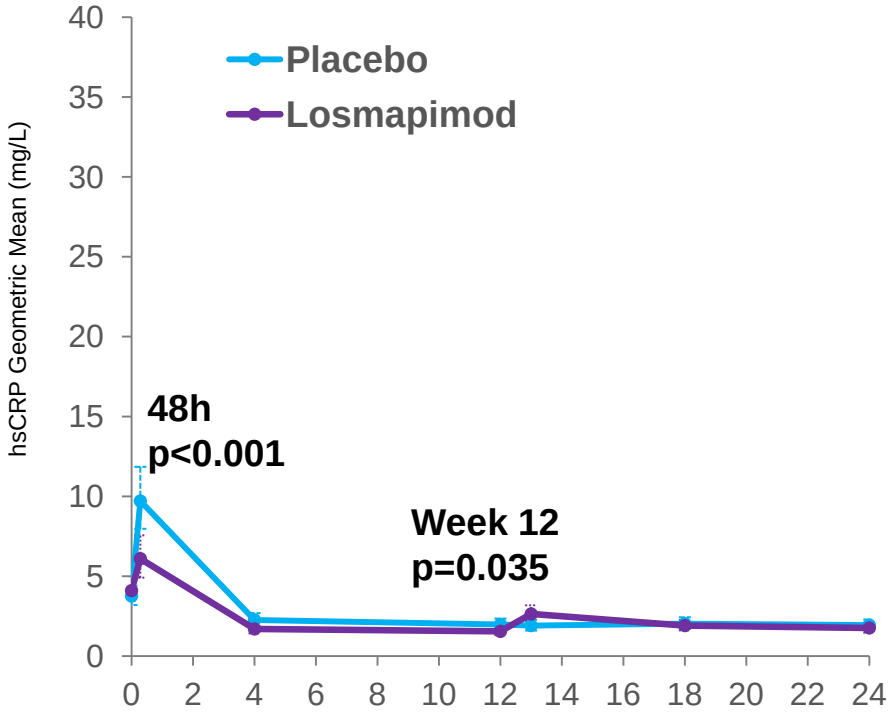
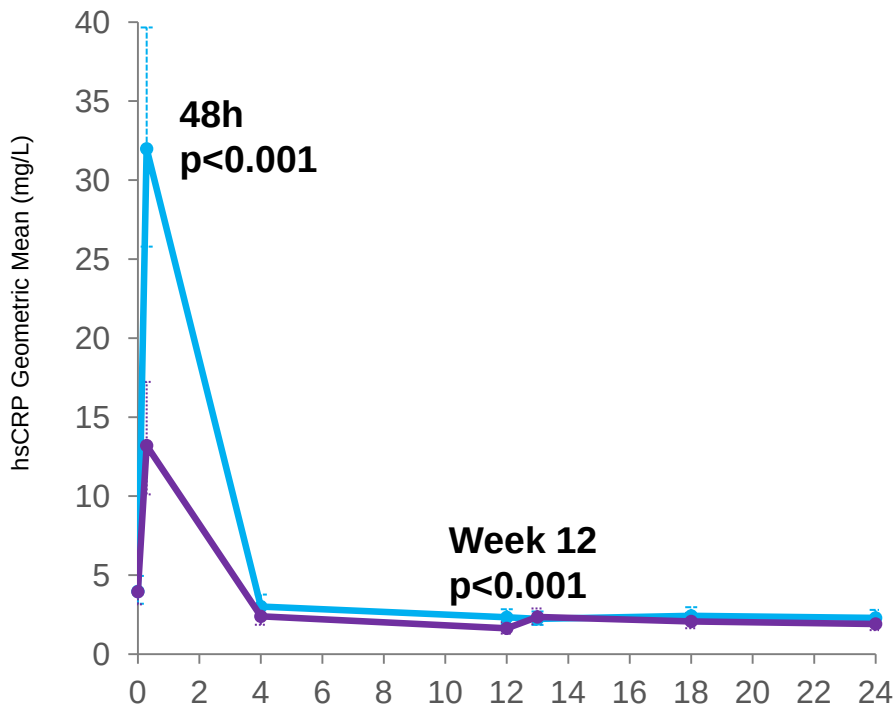
NSTEMI



P	210	187	198		193	156		176		179		
L	200	181	187		181	153		166		168		

STEMI



P	107	103	106		105	98		102		96		
L	114	108	109		107	91		98		95		

Error bars indicate 95% confidence intervals

NT-proBNP Cardiac Biomarker Substudy

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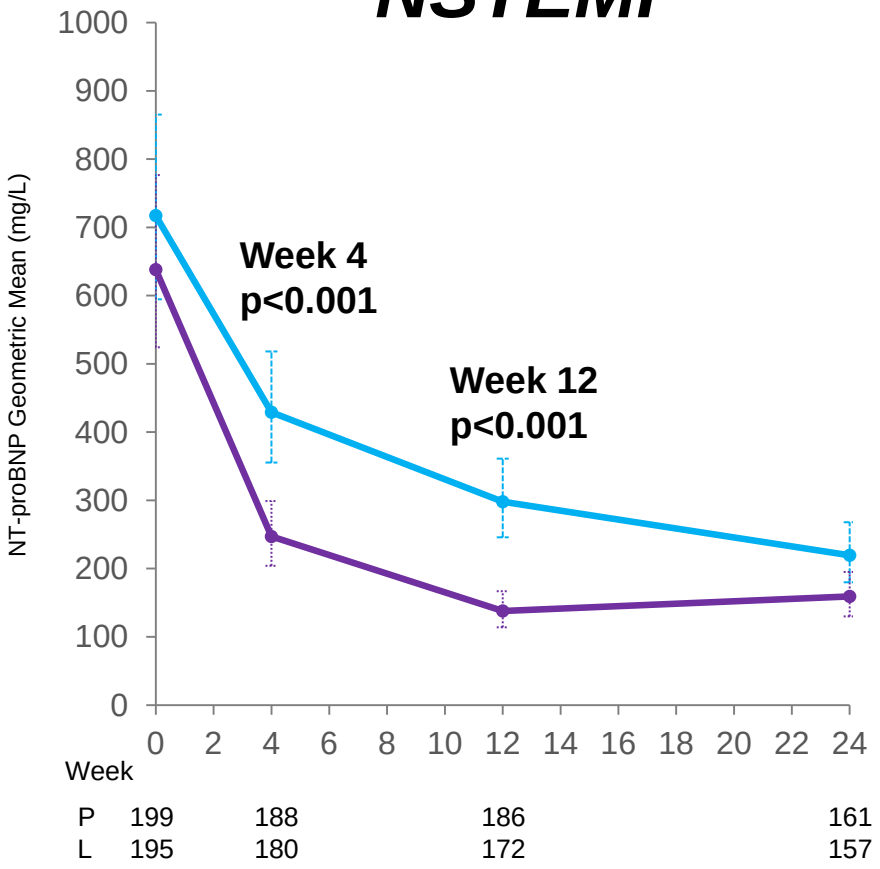
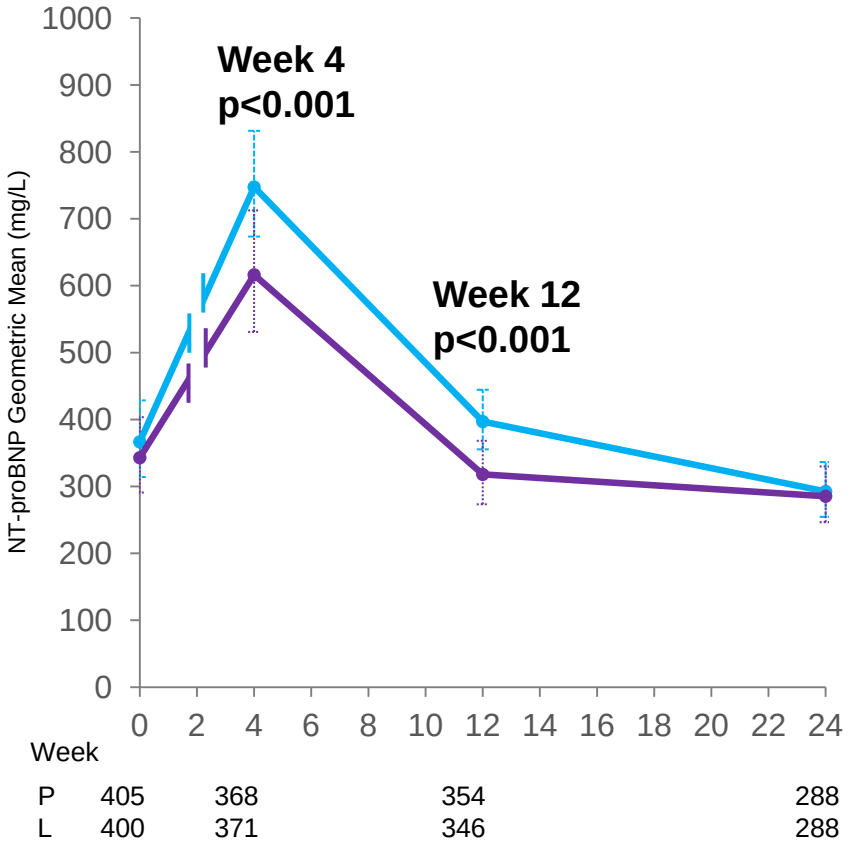
NSTEMI



P	199	188	186	161
L	195	180	172	157

STEMI

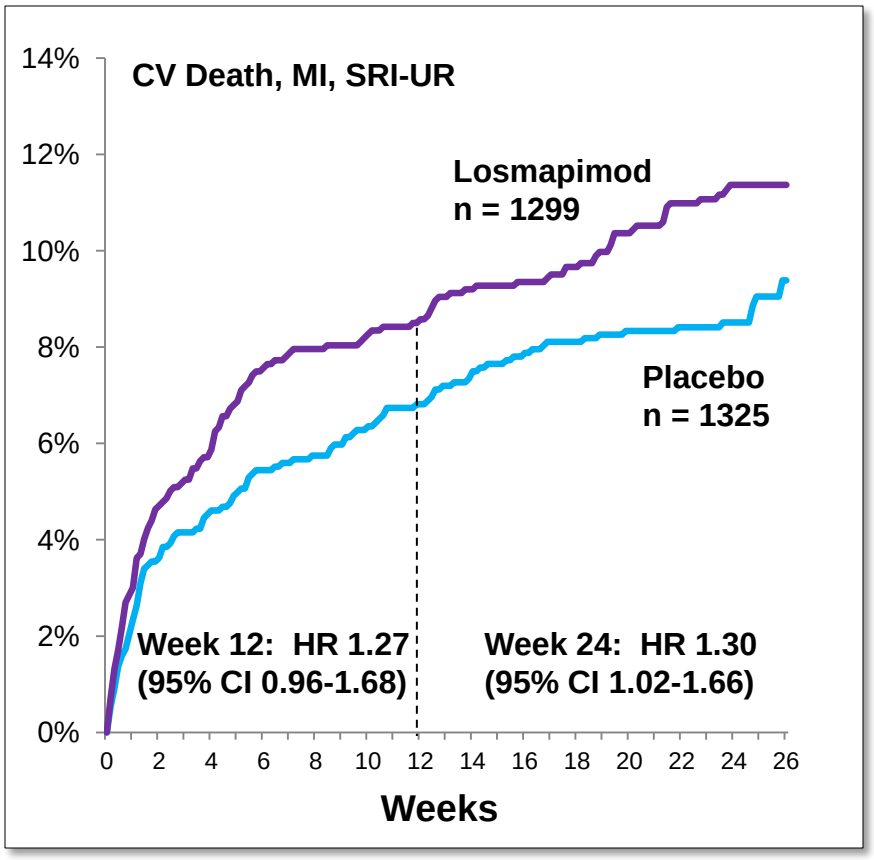


P	405	368	354	288
L	400	371	346	288

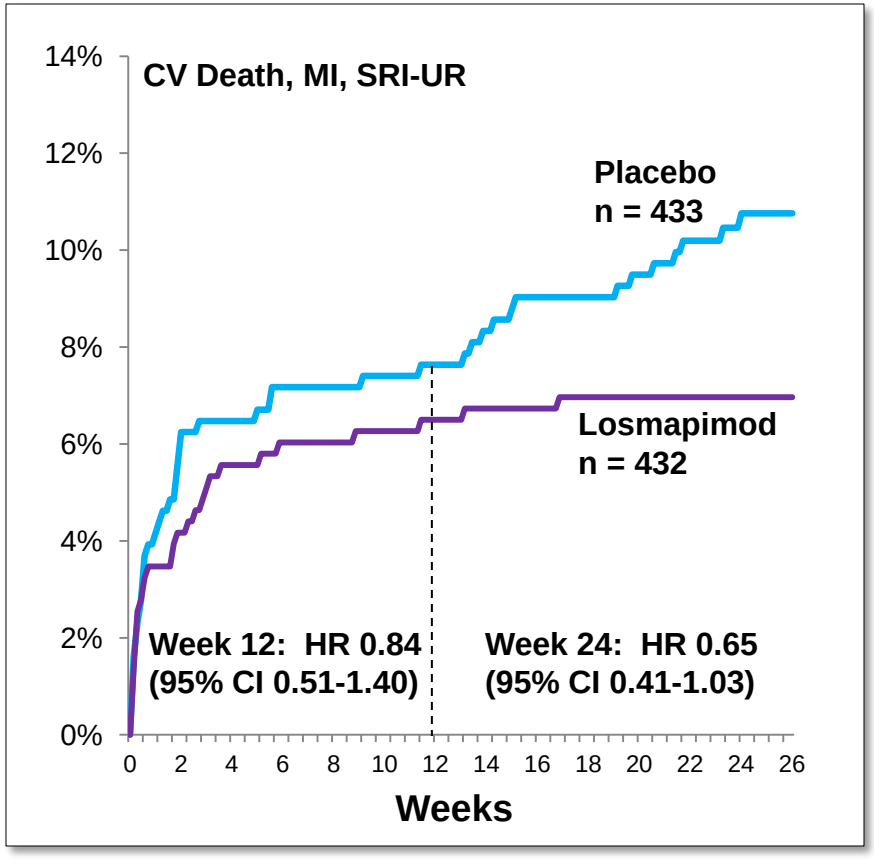
Error bars indicate 95% confidence intervals

MACE through Week 24 by Qualifying NSTEMI vs STEMI

NSTEMI



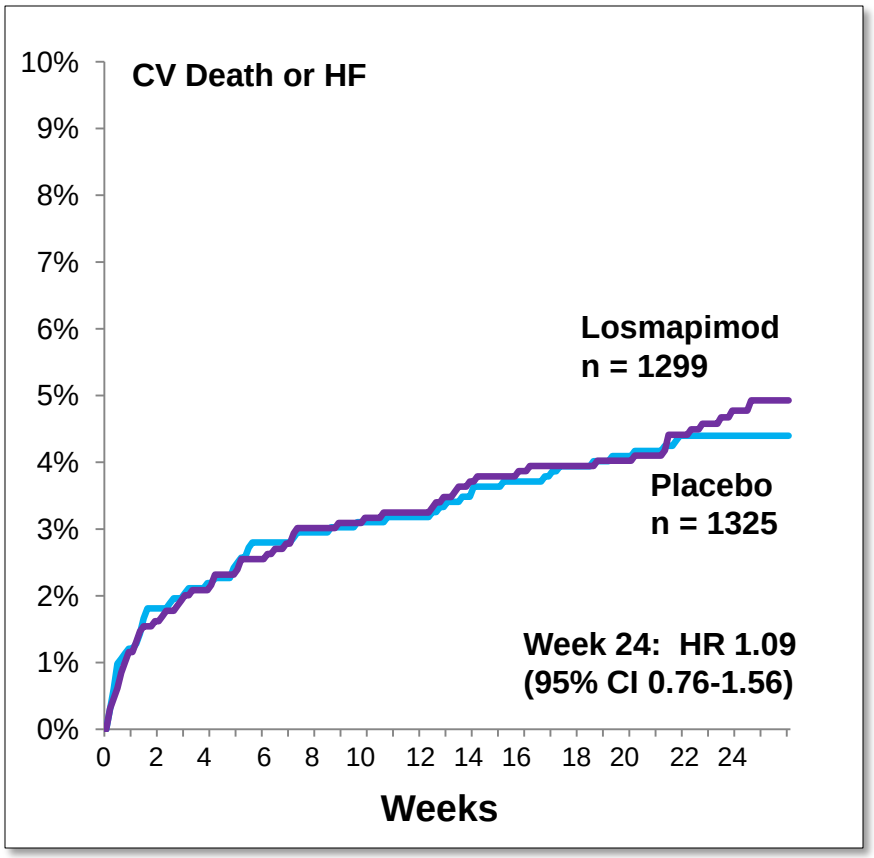
STEMI



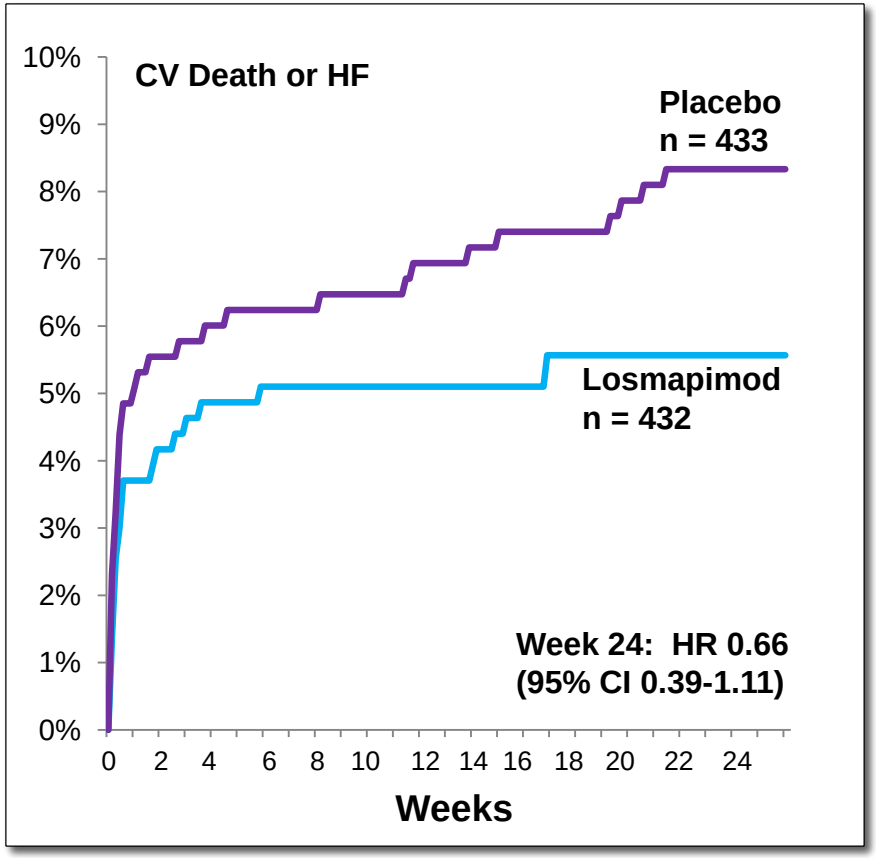
P-interaction = 0.009

CVD/HF through Week 24 by Qualifying STEMI vs NSTEMI

NSTEMI



STEMI



P-interaction = 0.12

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Summary

When administered in a broad population with acute MI for 12 weeks, losmapimod:

- Reduced inflammation measured with hsCRP
  - Blunting the acute inflammatory response to MI
  - Reducing chronic inflammation at 12 weeks
- Did not reduce the rate of recurrent major CV events
- Was generally well tolerated
- Yielded exploratory findings in STEMI worthy of additional investigation

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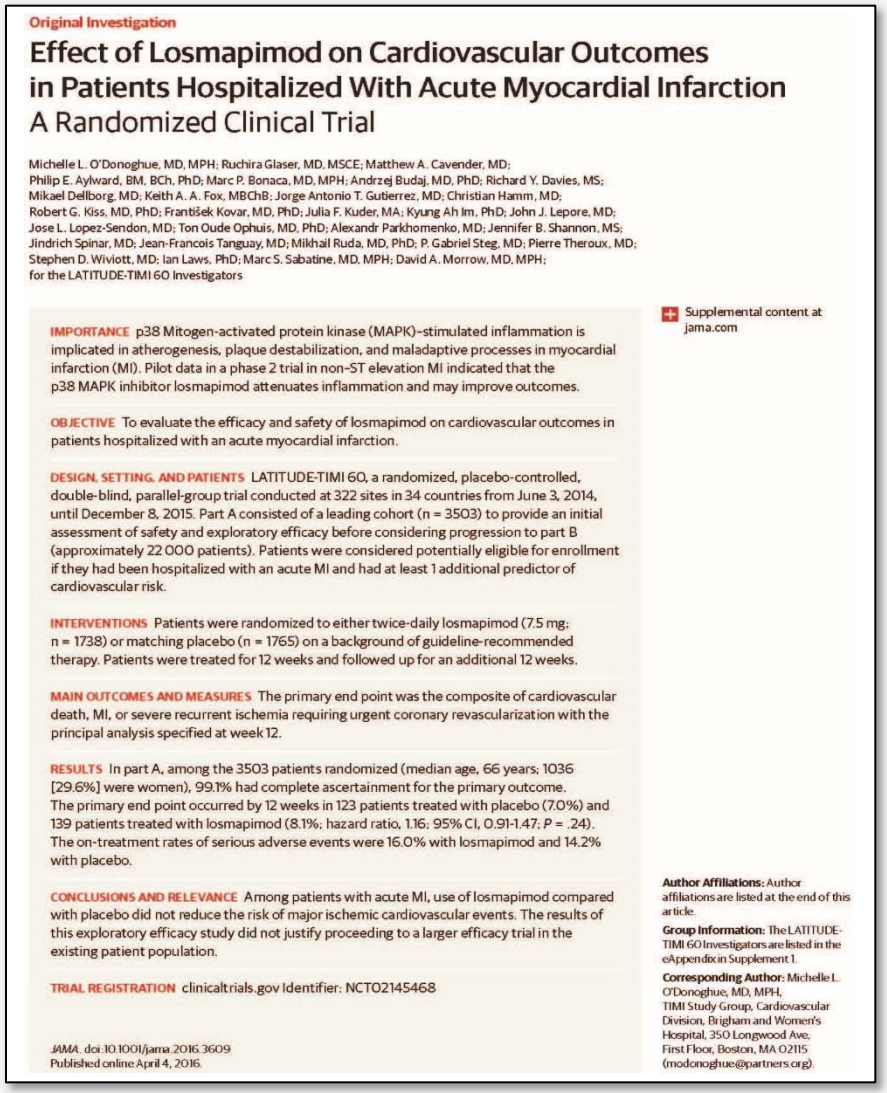
Scientific Implications

- Anti-inflammatory therapy with MAPK inhibition, despite reducing CRP, did not reduce CV events in patients hospitalized with acute MI
- Translation of direct modification of inflammatory pathways into CV clinical benefits has been elusive
  - Other trials of anti-inflammatory therapies in patients with cardiovascular disease are ongoing
- Use of an adaptive staged design allowed for preliminary insight into drug efficacy and safety and may serve as a model for future trials



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.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02145468

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The LATITUDE-TIMI 60 Investigators are listed in the eAppendix in Supplement 1.

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