Losmapimod To Inhibit p38 MAP kinase as a therapeutic target and modify outcomes after an acute coronary syndrome

NCT02145468 (www.clinicaltrials.gov)

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Losmapimod</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, RIUR, CVA or HF (%)</td>
<td>16.3</td>
<td>13.6</td>
</tr>
<tr>
<td>HR</td>
<td>0.82</td>
<td>(95% CI 0.49-1.37)</td>
</tr>
</tbody>
</table>

526 NSTEMI patients treated for 90d
**LATITUDE-TIMI 60**

**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)

Efficacy & Safety Assessment  
- TIMI  
- Sponsor  
- Independent Data Monitoring Committee  

Primary efficacy analysis would be based exclusively on Part B

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

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

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

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

N=3,503
Part A

Anticipated n~200 1° EP (Part A)
Trial Organization

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

Executive Committee
Marc S. Sabatine (Chair)  David A. Morrow (Global PI)
Philip Aylward  Keith Fox
José López-Sendón  P. Gabriel Steg
Pierre Theroux

Sponsor: GlaxoSmithKline
Ian Laws  Ruchira Glaser
Caroline Aitken & Katharine Edmunds  Allison Northcutt & Denise Fontanilla
Lea Sarov-Blat & Lalita Darooka  Jorge Ross & Curtis Rambaran
Richard Davies & Jennifer Shannon

Independent Data Monitoring Committee
Jeffrey L. Anderson (Chair)  James A. de Lemos
Kerry L. Lee  Freek W. A. Verheugt
W. Douglas Weaver
# National Lead Investigators

<table>
<thead>
<tr>
<th>ARGENTINA (42)</th>
<th>GREECE (76)</th>
<th>SLOVAKIA (231)</th>
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<tbody>
<tr>
<td>Rafael Diaz</td>
<td>Dimitrios Tziakas</td>
<td>Frantisek Kovar</td>
</tr>
<tr>
<td>AUSTRALIA (130)</td>
<td>Robert Kiss</td>
<td>SOUTH AFRICA (25)</td>
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<tr>
<td>Phil Aylward</td>
<td>Israel (38)</td>
<td>Anthony Dalby</td>
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<td>BELGIUM (72)</td>
<td>Basil Lewis</td>
<td>SOUTH KOREA (62)</td>
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<tr>
<td>Peter Sinnaeve</td>
<td>Italy (56)</td>
<td>Ki-Bae Seung</td>
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<td>BULGARIA (73)</td>
<td>Diego Ardissino</td>
<td>SPAIN (229)</td>
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<tr>
<td>Assen Goudev</td>
<td>Piera Merlini</td>
<td>Jose Lopez-Sendón</td>
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<tr>
<td>CANADA (66)</td>
<td>Netherlands (223)</td>
<td>SWEDEN (92)</td>
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<tr>
<td>Pierre Theroux</td>
<td>Ton Oude Ophuis</td>
<td>Mikael Dellborg</td>
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<tr>
<td>CHILE (33)</td>
<td>New Zealand (67)</td>
<td>Thailand (30)</td>
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<tr>
<td>Ramón Corbalán</td>
<td>Harvey White</td>
<td>Piyanitr Sritara</td>
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<tr>
<td>CZECH REPUBLIC (228)</td>
<td>Norway (39)</td>
<td>Ukraine (90)</td>
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<tr>
<td>Jindřich Špínar</td>
<td>Dan Atar</td>
<td>Alexander Parkhomenko</td>
</tr>
<tr>
<td>DENMARK (51)</td>
<td>Poland (215)</td>
<td>United Kingdom (62)</td>
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<tr>
<td>Jan Skov Jensen</td>
<td>Andrzej Budaj</td>
<td>Keith Fox</td>
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<tr>
<td>ESTONIA (99)</td>
<td>Romania (58)</td>
<td>Neal Uren</td>
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<tr>
<td>FRANCE (97)</td>
<td>Maria Dorobantu</td>
<td>United States (417)</td>
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<tr>
<td>Gabriel Steg</td>
<td>Russia (233)</td>
<td>Michelle O’Donoghue</td>
</tr>
<tr>
<td>GERMANY (186)</td>
<td>Mikhail Ruda</td>
<td></td>
</tr>
<tr>
<td>Christian Hamm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

34 countries  
322 sites  
3503 subjects

Complete flu was obtained in 99.4% of patients  
Only 1 patient was lost to follow up
## Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Losmapimod (N=1731)</th>
<th>Placebo (N=1758)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (IQR)</strong></td>
<td>66 (61-74)</td>
<td>67 (61-73)</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td><strong>White Race (%)</strong></td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td><strong>Median BMI (IQR)</strong></td>
<td>28 (25-31)</td>
<td>28 (25-31)</td>
</tr>
<tr>
<td><strong>Current Smoker (%)</strong></td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td><strong>History of Diabetes Mellitus (%)</strong></td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td><strong>Prior MI (%)</strong></td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td><strong>Prior Heart Failure (%)</strong></td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>Baseline eGFR ≤60ml/min/1.73m² (%)</strong></td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>
Details of Qualifying Event

- NSTEMI 75%
- STEMI 25%

INV 90%
- Invasive
- Conservative

PPCI 97%
- Primary PCI
- Fibrinolytic

62% of NSTEMI patients underwent PCI
# Time From Study Drug Administration to Coronary Revascularization

<table>
<thead>
<tr>
<th></th>
<th>Losmapimod</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSTEMI (hours, median, IQR)</td>
<td>1.7 (0.6-8.9)</td>
<td>1.8 (0.5-9.1)</td>
</tr>
<tr>
<td>STEMI (hours, median, IQR)</td>
<td>0.2 (0.1-0.6)</td>
<td>0.2 (0.0-0.6)</td>
</tr>
</tbody>
</table>
Inflammatory Response after ACS (Serial C-reactive protein)

- **Placebo**
- **Losmapimod**

**48h**: P < 0.001
**Week 4**: P = 0.01
**Week 12**: P < 0.001

Error bars indicate 95% confidence intervals.
Primary Endpoint (MACE) through Week 12

HR 1.16 (95% CI 0.91-1.47)
P value (log rank) = 0.24

CV death, MI or SRI-UR*

Losmapimod 8.1%
Placebo 7.0%

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

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

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

## Adverse Events

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

Abbreviation: ULN, upper limit normal
Subgroup Analyses: Primary Endpoint through Week 12

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

*SRI-UR: severe recurrent ischemia requiring urgent coronary revascularization
Serial hsCRP in NSTEMI & STEMI Cardiac Biomarker Substudy

**NSTEMI**

- Placebo
- Losmapimod

- 48h p<0.001
- Week 12 p=0.035

**STEMI**

- hsCRP Geometric Mean (mg/L)
- 48h p<0.001
- Week 12 p<0.001

Week
- P: 210 187 198
- L: 200 181 187
- 193 156 176
- 181 153 166
- 179 168
- 107 103 106
- 114 108 109
- 107 98 96
- Error bars indicate 95% confidence intervals
NT-proBNP
Cardiac Biomarker Substudy

**NSTEMI**

- Week 4: p<0.001
- Week 12: p<0.001

**STEMI**

- Week 4: p<0.001
- Week 12: p<0.001

Error bars indicate 95% confidence intervals
MACE through Week 24 by Qualifying NSTEMI vs STEMI

**NSTEMI**
- CV Death, MI, SRI-UR
- Losmapimod: n = 1299
- Placebo: n = 1325

Week 12: HR 1.27 (95% CI 0.96-1.68)
Week 24: HR 1.30 (95% CI 1.02-1.66)

**STEMI**
- CV Death, MI, SRI-UR
- Placebo: n = 433
- Losmapimod: n = 432

Week 12: HR 0.84 (95% CI 0.51-1.40)
Week 24: HR 0.65 (95% CI 0.41-1.03)

**P-interaction = 0.009**
CVD/HF through Week 24 by Qualifying STEMI vs NSTEMI

**NSTEMI**

- **CV Death or HF**
  - Losmapimod: n = 1299
  - Placebo: n = 1325
  - Week 24: HR 1.09 (95% CI 0.76-1.56)

**STEMI**

- **CV Death or HF**
  - Placebo: n = 433
  - Losmapimod: n = 432
  - Week 24: HR 0.66 (95% CI 0.39-1.11)

**P-interaction = 0.12**
Summary

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

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

O'Donoghue ML and coauthors

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

Published online April 4, 2016

Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com