Effect of REG1 Anticoagulation System versus Bivalirudin on Cardiovascular Outcomes Following PCI:

The REGULATE-PCI Randomized Clinical Trial

Roxana Mehran, John Alexander, and Michael Lincoff on the Behalf of the REGULATE-PCI Investigators
The trial was sponsored by Regado Biosciences

Conflicts of Interest:  R Mehran

Consulting:
• AstraZeneca; Bayer; CSL Behring; Janssen Pharmaceuticals, Inc.; Merck & Co., Inc.; Osprey Medical Inc.; Regado Biosciences, Inc.; The Medicines Company; Watermark Consulting

Scientific Advisory Board:
• Abbott Laboratories; AstraZeneca; Boston Scientific Corporation; Covidien; Janssen Pharmaceuticals, Inc.; Merck & Co., Inc.; The Medicines Company; sanofi-aventis

• Please visit websites https://www.mountsinai.org, https://www.dcrl.org, hppts://www.my.clevelandclinic.org for comprehensive disclosures for the institutions and investigators
Trial Organization

Academic Leadership

Executive Committee
- John Alexander (co-PI)
- Michael Lincoff (co-PI)
- Roxana Mehran (co-PI)
- Paul Armstrong
- Gabriel Steg
- Christoph Bode
- Steve Zelenkofske (Regado)

Steering Committee:
K. Huber (Austria), P.R. Sinnaeve (Belgium), Chris Buller (Canada), M. Aschermann (Czech Republic), P. Laanmets (Estonia), B. Merkely (Hungary), V. Guetta (Israel), M. Valgimigli (Italy), J.H. Cornel (Netherlands), J.D. Kasprzak (Poland), J. Morais (Portugal), B. Alekyan (Russia), V. Fridrich (Slovakia), J. Lopez/Sendon (Spain), R. Stables (UK), M.G. Cohen (USA), T. Povsic (USA), A. Levinson (USA), R. Becker (USA), V. Hasselblad (USA).

Operations

Project Management: DCRI, C5R, Regado, PAREXEL
US Site Management: DCRI, C5R
CN Site Management: CVC
ROW Site Management: PAREXEL
Data Management: DCRI
Statistics: DCRI
Safety: DCRI
Clinical Event Committee: DCRI
IXRS: ClinPhone Perceptive Informatics
Study Drug: Catalent / PAREXEL
DSMB: Stanford U. – Robert Harrington (chair)
• Refinements in antithrombotic therapies have considerably enhanced the efficacy and safety of percutaneous coronary intervention (PCI), although no optimal strategy yet exists.

• Platelet glycoprotein IIb/IIIa receptor antagonists reduce ischemic complications, but are accompanied by increased bleeding with associated mortality, morbidity and medical resource cost.

• Bivalirudin reduces the risk of bleeding compared to heparin and glycoprotein IIb/IIIa inhibition, but is associated with higher rates of stent thrombosis and trends to more periprocedural myocardial infarction.

What would be an ideal antithrombotic Regimen for PCI?

• Rapid Onset of Action
• Predictable Dose-Response

1-Journal of the American College of Cardiology 2011;57:1190-9
3-American Heart Journal 2008;155:369-74
The REG1 Anti-Coagulation System

Factor IXa

pegnivacogin (RB006)

pegnivacogin
Anticoagulant aptamer
- Specific affinity for Factor IXa

anivamersen (RB007)

- Specific affinity for pegnivacogin with no other activity

anivamersen
Active control agent

4-Circulation 2008;117:2865-74.
5-European Heart Journal (2013) 34, 2481–2489
REG1 In the RADAR Trial

- The phase 2, randomized, active-controlled RADAR trial showed that with at least 50% reversal of pegnivacogin by anivamersen, early vascular sheath removal was feasible and bleeding rates similar to heparin.

- The composite of 30-day death, non-fatal MI, urgent target vessel revascularization, or recurrent ischemia in the target vessel was numerically lower in patients assigned to REG1 than Heparin (OR: 0.5; 95% CI: 0.2 – 1.4; p = 0.1). The majority of ischemic events were non-fatal periprocedural MIs.

- In the RADAR study, 3 patients had allergic-like reactions shortly after pegnivacogin administration, of which 2 of these reactions were serious.
The REGULATE-PCI Randomized Clinical Trial

- Randomized, open-label, active-controlled, superiority, phase 3 trial to test the hypothesis that near complete FIXa inhibition with Pegnivacogin during PCI would provide a greater reduction in ischemic events than bivalirudin without increased bleeding as a result of anticoagulant reversal with Anivamersen.
Study Scheme

Angiography/Need for PCI

Open-Label 1:1 Randomization

REG1 Arm

Pegnivacogin 1 mg/kg

Anivamersen 0.5 mg/kg

Primary Outcome (Day 3)

FU Assessment 4-10d

FU Visit 30d

Bivalirudin Arm

Dose

PCI

End of PCI

Sheath removal

Bival Bolus

Bival Infusion

Primary Outcome (Day 3)
Inclusion Criteria

- Patients with CAD undergoing PCI stratified by 3 key subgroups:
  - **Subgroup A**: Patients with MI within prior 7 days - ischemic symptoms at rest and **positive cardiac biomarkers**
  - **Subgroup B**: Patients with **at least one of the following risk factors**: ACS with positive cardiac biomarkers > 7 days prior to randomization; unstable angina (without positive cardiac biomarkers); age > 70 years; diabetes; chronic kidney disease (estimated CrCl < 60 mL/min); planned multivessel PCI; prior CABG surgery; peripheral vascular disease;
  - **Subgroup C**: Patients with **negative cardiac biomarkers and no risk factor**, thereby not meeting criteria for Subgroup A or B.

- Enrollment began with approximately 1000 patients from Subgroups B and C, with expansion to include the Subgroup A only after the safety of REG1 in lower-risk patients had been established.
Prior to randomization  Investigators had to specify femoral or radial access and

- Vascular Closure Device use (yes/no)
- Planned target vessel(s)
- ADP/P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor).
Study Drug Administration

REG1 Arm

- **Pegnivacogin**, bolus injection of 1.0 mg/kg over 2 minutes IV or via arterial sheath just prior to PCI procedure
- **Anivamersen**, 0.5 mg/kg (80% reversal) IV over 1 minute upon completion of PCI.
  - Second complete reversal dose of anivamersen (i.e. 0.5 mg/kg) to achieve 100% reversal could be administered at any time post PCI for bleeding

Bivalirudin Arm

- Bolus injection of 0.75 mg/kg over 2 minutes IV or via arterial sheath just prior to the PCI procedure, followed by IV infusion of 1.75 mg/kg/hour (or per local label depending on renal function) until completion of the procedure
  - Infusion discontinued upon completion of the PCI procedure

- Aspirin + P2Y12-Inhibitor for all patients prior to PCI.
- GPI could be used only provisionally for procedural or angiographic complications
ENDPOINTS
(Assessed at 3 and 30 Days)

Primary Efficacy Endpoint
- Composite of death, non-fatal MI, non-fatal stroke and urgent TLR through Day 3.

Primary Safety Endpoint
- Incidence of bleeding (BARC 3 or 5; not related to CABG) through Day 3;
- Components of the primary endpoint through day 3
- Composite of death, non-fatal MI, non-fatal stroke and urgent TLR through day 30
- Bleeding endpoints through day 30
- Incidence and severity of allergic adverse events.

Secondary Endpoints

Efficacy analyses were based upon the intention-to-treat population, with the test of the null hypothesis based on the odds ratio and two-sided 95% CI from the Cochran-Mantel-Haenszel test with risk subgroup (Subgroup A, B, or C) as the stratification factor.

Superiority Trial Design with an expected risk reduction of 20% for the primary efficacy endpoint.

Anticipated 830 adjudicated events, providing an 90% power for a two-sided alpha less than or equal to 0.049 with one planned interim efficacy review at 50% enrollment.

Endpoint Estimations:

Primary endpoint event rate of 7.0% in the Bivalirudin arm (8% in Subgroup A, 6% in Subgroups B and C)

Primary endpoint event rate of 5.6% in the REG1 arm.

Estimated sample size of 13,200 patients, of whom at least 6600 were to be enrolled from Subgroup A. Secondary endpoints were to be evaluated using a hierarchical closed testing procedure to preserve overall Type I error.
<table>
<thead>
<tr>
<th>Date</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 13, 2013</td>
<td>Initial recruitment in the trial</td>
</tr>
<tr>
<td>April 2, 2014</td>
<td>Enrollment expanded to include patients in Subgroup A after review of</td>
</tr>
<tr>
<td></td>
<td>safety among the first approximately 1000 patients.</td>
</tr>
<tr>
<td>June 29, 2014</td>
<td>Ongoing evaluation of reports of severe allergic reactions</td>
</tr>
<tr>
<td></td>
<td>Sponsor and executive committee suspended enrollment</td>
</tr>
<tr>
<td></td>
<td>A total of 3232 of the planned 13,200 patients had been enrolled</td>
</tr>
<tr>
<td></td>
<td>hospitals in North America and Europe.</td>
</tr>
<tr>
<td>August 21, 2014</td>
<td>DSMB recommended permanent termination of the trial with excess rates</td>
</tr>
<tr>
<td></td>
<td>of allergic reactions with REG1 without evidence of offsetting benefit.</td>
</tr>
</tbody>
</table>

**REGULATE PCI Enrollment**

- September 13, 2013: Initial recruitment in the trial.
- April 2, 2014: Enrollment expanded to include patients in Subgroup A after review of safety among the first approximately 1000 patients.
- June 29, 2014: Ongoing evaluation of reports of severe allergic reactions.
  - Sponsor and executive committee suspended enrollment.
  - A total of 3232 of the planned 13,200 patients had been enrolled at 225 hospitals in North America and Europe.
- August 21, 2014: DSMB recommended permanent termination of the trial based on findings of excess rates of allergic reactions with REG1 without evidence of offsetting benefit.
### Top 5 Enroller Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>N. Of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1965</td>
</tr>
<tr>
<td>Canada</td>
<td>288</td>
</tr>
<tr>
<td>Estonia</td>
<td>174</td>
</tr>
<tr>
<td>Italy</td>
<td>131</td>
</tr>
<tr>
<td>Slovakia</td>
<td>124</td>
</tr>
</tbody>
</table>

**17 Participating Countries**
# Top 5 Enroller Centers

<table>
<thead>
<tr>
<th>Country</th>
<th>Investigator</th>
<th>Center</th>
<th>N. Of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 United States</td>
<td>J. Tauth</td>
<td>HS Cardiology Associate (Hot Springs National Park, AR)</td>
<td>304</td>
</tr>
<tr>
<td>2 United States</td>
<td>G. Soliman</td>
<td>Heart Center, Inc. (Huntsville, AL)</td>
<td>148</td>
</tr>
<tr>
<td>3 Estonia</td>
<td>T. Marandi</td>
<td>University of Tartu (Tartumaa, Eesti)</td>
<td>134</td>
</tr>
<tr>
<td>4 Canada</td>
<td>W. Cantor</td>
<td>Southlake Regional Health Centre, (Newmarket, ON)</td>
<td>123</td>
</tr>
<tr>
<td>5 Slovakia</td>
<td>M. Hranai</td>
<td>Národný, Oddelenie Intervenčnej Kardiológie</td>
<td>123</td>
</tr>
</tbody>
</table>
STUDY CONSORT DIAGRAM

Randomized (n=3232)

Allocated to REG1 (n=1616)
- Received REG1 (n=1605)
- Underwent index PCI (n=1605)
- Received REG1 and underwent index PCI (n=1602)
- Did not receive REG1 (n=11)*

Allocated to Bivalirudin (n=1616)
- Received Bivalirudin (n=1601)
- Underwent index PCI (n=1607)
- Received Bivalirudin and underwent index PCI (n=1598)
- Did not receive study drug Bivalirudin (n=15)†

Lost to follow-up (n=1):‡ Unable to contact (n=1)

Lost to follow-up (n=3):‡ Unable to contact (n=3)

Lost to follow-up (n=3):‡ Unable to contact (n=1) Withdrawed consent (n=1) Unknown (n=1)

Lost to follow-up (n=8):‡ Unable to contact (n=5) Withdrawed consent (n=2) Unknown (n=1)

Analysed (n=1616)
- Excluded from analysis (n=0)
- Endpoint imputed (n=3)

Analysed (n=1616)
- Excluded from analysis (n=0)
- Endpoint imputed (n=8)
### BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>REG1 (N = 1616)</th>
<th>Bivalirudin (N = 1616)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - mean, years</td>
<td>65 +/- 11</td>
<td>65 +/- 11</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>1215 (75)</td>
<td>1184 (73)</td>
</tr>
<tr>
<td>Diabetes mellitus – no. (%)</td>
<td>571 (35)</td>
<td>553 (34)</td>
</tr>
<tr>
<td>Body mass index – mean, kg/m2</td>
<td>30 +/- 6</td>
<td>30 +/- 6</td>
</tr>
<tr>
<td>Prior myocardial infarction – no. (%)</td>
<td>576 (36)</td>
<td>582 (36)</td>
</tr>
<tr>
<td>Prior PCI – no. (%)</td>
<td>818 (51)</td>
<td>850 (53)</td>
</tr>
<tr>
<td>Prior coronary bypass surgery – no. (%)</td>
<td>278 (17)</td>
<td>265 (16)</td>
</tr>
<tr>
<td>Prior stroke – no. (%)</td>
<td>67 (4)</td>
<td>68 (4)</td>
</tr>
<tr>
<td>Left ventricular dysfunction (EF &lt;55%) – no. (%)</td>
<td>553 (38)</td>
<td>594 (41)</td>
</tr>
<tr>
<td>Current tobacco use – no. (%)</td>
<td>348 (22)</td>
<td>322 (20)</td>
</tr>
<tr>
<td>History of any allergies – no. (%)</td>
<td>520 (32)</td>
<td>538 (33)</td>
</tr>
<tr>
<td>Randomization stratification subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup A</td>
<td>246 (15)</td>
<td>247 (15)</td>
</tr>
<tr>
<td>Subgroup B</td>
<td>1101 (68)</td>
<td>1100 (68)</td>
</tr>
<tr>
<td>Subgroup C</td>
<td>269 (17)</td>
<td>269 (17)</td>
</tr>
</tbody>
</table>
• Vascular closure devices used in ≈32% of patients in both randomization arms
Stent Used During PCI

REG-1
- DES: 81%
- BMS: 16%
- DES and BMS: 3%

Bivalirudin
- DES: 81%
- BMS: 17%
- DES and BMS: 2%
Platelet P2Y12 Antagonist Therapy After PCI

- 99% treated with Aspirin in both randomization arms
# ALLERGIC EVENTS

<table>
<thead>
<tr>
<th>End Point by Day 3</th>
<th>REG1 (N = 1605)</th>
<th>Bivalirudin (N = 1601)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious Allergic Events</strong></td>
<td>10 (0.6)</td>
<td>1 (&lt; 0.1)</td>
</tr>
<tr>
<td>Fatal Event</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Severe Event (Anaphylactic Reaction)</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td><strong>Organ System Involvement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Circulatory</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>GI or GU</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Non-Serious Allergic Events</strong></td>
<td>14 (0.9)</td>
<td>9 (0.5)</td>
</tr>
<tr>
<td>Severe Event (Anaphylactic Reaction)</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Non-Severe Event</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
EFFICACY ENDPOINTS (Day 3)

1° Endpoint

Death, MI, Stroke or Urgent TLR

- REG-1: 6.7%
- Bivalirudin: 6.4%

P = 0.72

Death

- REG-1: 6.4%
- Bivalirudin: 5.8%

P = 0.46

Myocardial Infarction

- REG-1: 0.1%
- Bivalirudin: 0.2%

P = 0.32

Stroke

- REG-1: 0.1%
- Bivalirudin: 0.5%

P = 0.25

Urgent Target Lesion Revascularization

- REG-1: 0.2%
- Bivalirudin: 0.1%

P = 0.06

Stent Thrombosis

- REG-1: 0.3%
- Bivalirudin: 0.4%

P = 0.26
EFFICACY ENDPOINTS (Day 30)

- **Death, Myocardial Infarction, Stroke or Urgent Target Lesion Revascularization**
  - REG-1: 7.5%
  - Bivalirudin: 7.5%
  - P = 1.00

- **Death**
  - REG-1: 0.5%
  - Bivalirudin: 0.7%
  - P = 0.36

- **Myocardial Infarction**
  - REG-1: 6.8%
  - Bivalirudin: 6.4%
  - P = 0.69

- **Stroke**
  - REG-1: 0.2%
  - Bivalirudin: 0.2%
  - P = 0.71

- **Urgent Target Lesion Revascularization**
  - REG-1: 0.4%
  - Bivalirudin: 1.0%
  - P = 0.06

- **Stent Thrombosis**
  - REG-1: 0.1%
  - Bivalirudin: 0.8%
  - P < 0.01

REG-1 and Bivalirudin were compared for their efficacy endpoints on Day 30.
BLEEDING SAFETY ENDPOINTS

Bleeding Rates by Day 3

- Major or Minor Non-CABG Bleeding (BARC Types 2, 3 or 5): REG-1 6.5%, Bivalirudin 4.1%, P = 0.002
- GUSTO Severe Non-CABG Bleeding: REG-1 0.4%, Bivalirudin 0.1%, P = 0.32
- TIMI Major Non-CABG Bleeding: REG-1 0.1%, Bivalirudin 0.1%, P = 0.57

Bleeding Rates by Day 30

- Major Non-CABG Bleeding (BARC Types 3 or 5): REG-1 7.6%, Bivalirudin 4.8%, P = 0.001
- GUSTO Severe Non-CABG Bleeding: REG-1 0.7%, Bivalirudin 0.3%, P = 0.99
- TIMI Major Non-CABG Bleeding: REG-1 0.3%, Bivalirudin 0.1%, P = 0.26

*Major Non-CABG Bleeding (BARC Types 3 or 5)
### Subgroup Analysis
Primary Efficacy Endpoint and Major Bleeding

#### Primary Efficacy Endpoint

<table>
<thead>
<tr>
<th>Interaction P-Value</th>
<th>Odds Ratio (95% CI)</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6029</td>
<td>0.91 (0.48-1.70)</td>
<td>2739</td>
</tr>
<tr>
<td></td>
<td>1.09 (0.80-1.49)</td>
<td>2739</td>
</tr>
</tbody>
</table>

Randomization Stratification Subgroups
- **Subgroup A**
- **Subgroup B/C**

Demographics
- **Gender**
  - Male
  - Female
- **Age**
  - ≤ 70 yrs
  - < 70 yrs

Region
- North America
- Europe

Renal Insufficiency
- **LV Function**
  - < 40%
  - ≥ 40%

Access Site
- **Radial**
- **Femoral**

Sheath Size
- **(largest arterial sheath)**
  - > 6 French
  - ≤ 6

P2Y12 Inhibitor Taken at Baseline
- **Yes**
- **No**

Type of P2Y12 Inhibitor
- Clopidogrel
- Ticagrelor
- Prasugrel

Anticoagulation at Baseline
- **Yes**
- **No**

#### Major Bleeding

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Odds Ratio (95% CI)</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>487</td>
<td>7.03 (0.86-57.22)</td>
<td>0.9640</td>
</tr>
<tr>
<td>2719</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No significant interactions in the primary efficacy and safety endpoint
LIMITATIONS

- Given the early termination of the trial with only 211 of the planned 830 primary endpoint events accrued, any conclusion regarding the safety in bleeding and efficacy in ischemic events of REG1 compared with Bivalirudin has to be considered exploratory.

- Open label design- Independent CEC blinded to treatment allocation was put forth to minimize bias in endpoint adjudication.
CONCLUSIONS

• In patients undergoing PCI, REG1 Anticoagulation System is associated with similar incidence ischemic events, but more moderate/severe (BARC 2,3,5) bleeding compared to Bivalirudin monotherapy.

• The reversible factor IXa inhibitor REG1, as currently formulated, is associated with an infrequent but unacceptably high rate (0.6%) of severe allergic reactions.

• Future investigations are planned to identify the mechanism of allergic reactions associated with REG1 Anticoagulation System.