First Human Use of a Novel Subcutaneous Platelet GPIIb/IIIa Inhibitor (RUC-4) Designed for STEMI Point of Care Treatment

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Background

- Despite national initiatives that have reduced median D2B times to <60 minutes, mortality from STEMI has plateaued[1]
- Focus has turned to total ischemic time as better correlate of infarct size/outcomes.
- "The primary opportunity for reducing total ischemic time and time to treatment and for improving outcomes, now lies in the pre-hospital STEMI system of care"[2]
- Early thrombus-platelet rich/late thrombus-fibrin-rich; GPIIb/IIIa inhibitors produce dose-dependent disaggregation of platelet-rich thrombus[3]

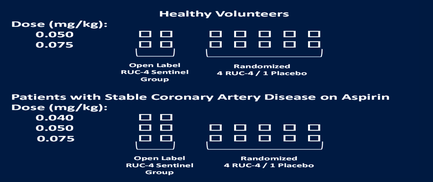
Challenges with Current Pre-Hospital Therapies

- Fibrinolytics treat fibrin-rich clot, have higher bleeding risk; are not readily given in ambulance.
- Approved GPIIb/IIIa inhibitors are parenteral (IV bolus-infusion); difficult in urgent situations/ ambulance setting.
- Oral P2Y12 inhibitors are not rapid/uniform in effect; poorly absorbed during STEMI. IPA is delayed and less intense.

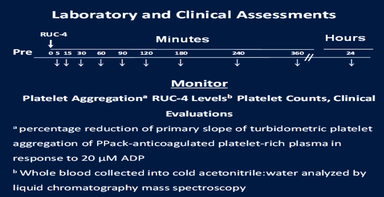
RUC-4: Unique GpIIb/IIIa Inhibitor

- Small molecule designed to inhibit fibrinogen-platelet binding and platelet aggregation.
- Locks GPIIb/IIIa receptor in inactive conformation (less thrombocytopenia and greater efficacy).
- Active with SC administration (not parenteral), highly soluble (total dose <1.0 ml) which facilitates auto-injector delivery

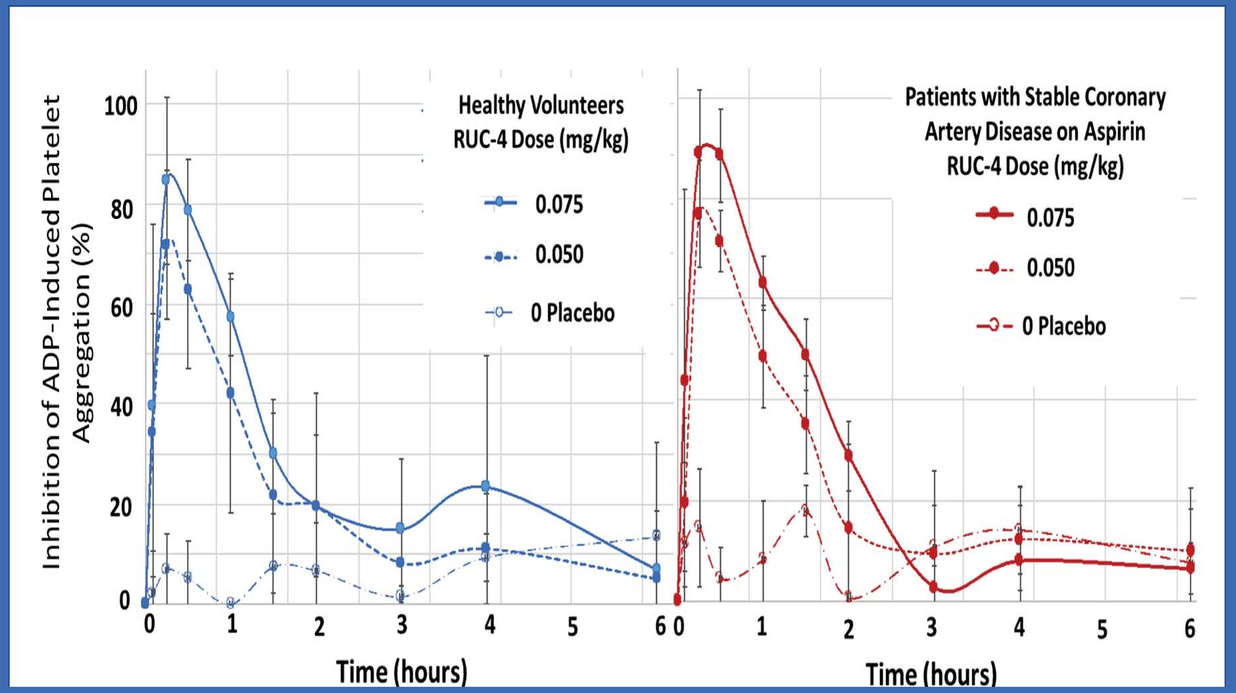
First Human Use Trial Design



Testing Assessments



RUC-4 provides rapid (<15 min), intense (>80%), short-term (<2 hours) inhibition of platelet aggregation after SC treatment without bleeding, thrombocytopenia or significant injection site reactions.



- Aspirin does not significantly affect RUC-4 PK, PD, or bleeding
- RUC-4 is an attractive candidate for first point of contact therapy of STEMI

Study Objective

Primary Objectives:

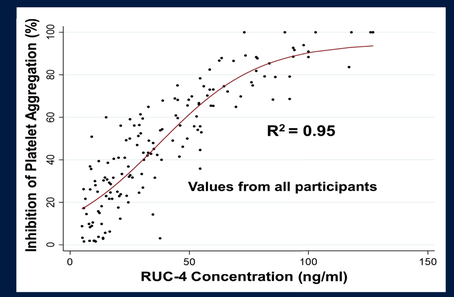
· Assess safety and tolerability of RUC-4 administered subcutaneously (SC) in healthy volunteers and subjects on aspirin with stable coronary artery disease (CAD) at escalating doses until a weight-adjusted (mg/kg) biologically effective dose (BED)* or maximum tolerated dose (MTD) is identified.

Secondary Objectives:

· Assess the pharmacokinetics (PK) and pharmacodynamics (PD) of escalating doses of RUC-4 administered SC in healthy volunteers and subjects on aspirin with stable CAD until a weight adjusted (mg/kg) BED or MTD is reached.

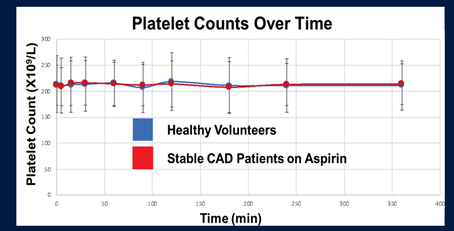
* Dose of RUC-4 leading to ≥80% inhibition of ADP-induced platelet aggregation within 15 minutes of SC administration with return toward baseline values ≤ 4 hours

Correlation Between IPA and RUC-4 Concentration



Safety Measures

- All injection site reactions were mild except one that was moderate
- No bleeding events
- No drug-related ECG changes
- No serious adverse events (SAEs)
- No drug-related changes in laboratory values
- Platelet counts stable



[1]Menees et al, *N Eng J Med* 2013; 369:901-9. [2]Bates, E. Jacobs, A. *N Eng J Med* 2013; 369(10):889-92, [3]Speich, HE. et al. *J Thromb Thrombolysis* (2013) 36:31–41

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Drs Kereiakes, DeMaria and Henry receive consulting fees from Celecor.
Dr Coller is Co-Inventor of RUC-4; equity holder in CeleCor; paid consultant to CeleCor. Co-Inventor of abciximab (Centocor/Janssen); in accord with federal law and policies of the Research foundation of the State University of New York, receives royalties for the sales of abciximab. Co-Inventor of VerifyNow assays(Accumetrics/Instrumentation Labs) and receives royalties for the sales of the VerifyNow assays. Dr. Coller served as a non-voting scientific consultant to the RUC-4 Safety Review Committee, but did not participate in identifying or adjudicating adverse events.