International PNH Interest Group Annual Meeting

American Society of Hematology Scientific Sessions
Manchester Grand Hyatt, San Diego CA
Friday 2\textsuperscript{nd} December 2016
Introducing RA101495: A Novel Subcutaneously-Administered Peptide Inhibitor of C5 for PNH

- Blocks C5 cleavage and production of C5a and C5b
- Phase 1 data in healthy volunteers shows rapid, complete, and sustained inhibition of ex vivo hemolysis
- Distinct from eculizumab binding site allows treatment of patients with R885H/C mutations
- Blocks interaction of C5b with C6 to prevent MAC assembly
  - May be beneficial in hypercoagulative states where thrombin or other proteases can cleave C5
- Administered by subcutaneous self-injection
  - Potential for increased convenience, freedom, and flexibility for patients
Suppression of hemolysis and complement activity was rapid, near-complete and sustained across the dosing period in all subjects.

Inhibition of hemolysis activity at D8 (24h after receiving the last dose) was observed to be ≥97% in all subjects.

Hemolysis activity returned to pre-dose levels within two weeks following the last dose.

n=2 (placebo) or 4 (0.2 mg/kg RA101495) dosed daily per group.

EHA 2016; Abstract #LB2249
# RA101495: Planned Phase 2 Design

## Cohort A (naïve)
- **n=8-12**
- **D1**
  - 0.3mg/kg, q.d. loading dose
- **W2**
  - 0.1mg/kg, q.d.
- **W6**
  - 0.1mg/kg, q.d. or up-titrate to 0.3mg/kg
- **W12**
  - 0.1mg/kg, q.d. or up-titrate to 0.3mg/kg
- Review of safety & efficacy
- Evaluation period for primary efficacy endpoint (change in LDH from baseline to mean of W6-12)

## Cohort B (switch)
- **n=6-8**
- **D1**
  - 0.3mg/kg, q.d. loading dose
- **W2**
  - 0.1mg/kg, q.d.
- **W6**
  - 0.1mg/kg, q.d. or up-titrate to 0.3mg/kg
- **W12**
  - 0.1mg/kg, q.d. or up-titrate to 0.3mg/kg
- Review of safety & efficacy
- Evaluation period for primary efficacy endpoint (change in LDH from baseline to mean of W6-12)

## United States

### Inadequate Responders (LDH > 1.5xULN)
- **n=6-8**
- **D1**
  - 0.3mg/kg LD
- **W2**
  - 0.1mg/kg, q.d.
- **W6**
  - 0.1mg/kg, q.d. or up-titrate to 0.3mg/kg
- **W12**
  - 0.1mg/kg, q.d. or up-titrate to 0.3mg/kg
- Review of safety & efficacy
- Evaluation period for primary efficacy endpoint (change in LDH from baseline to mean of W6-12)
0.3 mg/kg Load + 0.1 mg/kg q.d.: Predicted to Achieve Rapid, Complete, and Sustained Inhibition of Hemolysis

- blue: plasma level
- red: %inh

0.3 mg/kg Loading + 0.1 mg/kg q.d.
0.1 mg/kg q.d.: Expected to Maintain Inhibition of Hemolysis at all Times in all Patients
RA101495 Protects Against Complement-Mediated Hemolysis of Type III PNH Erythrocytes

Dose response

Drug concentration

No drug

RA101495

No drug

Eculizumab

Approx. 1 μM RA101495 or Ecu (Note: Ecu is bivalent)

Flow cytometry

Serum*

Serum + HCl

Serum + HCl + Eculizumab (1 μM)

Serum + HCl + RA101495 (1.2 μM)

*18h incubation of PNH RBCs with 50% acidified serum. PNH RBCs provided by Dr. Jaroslaw Maciejewski (CCF IRB 5024)
Series of orally bioavailable (%F>30) small molecules that bind C5, inhibit its cleavage/activation (IC\textsubscript{50} 14 nM in high sensitivity sheep RBC lysis assay), and prevent hemolysis of PNH erythrocytes in a dose dependent manner.

High resolution co-crystal structures of SM inhibitors bound to C5 available
- Complete understanding of mechanism of action
- Enables structure-guided optimization

*18h incubation of PNH RBCs with 50% acidified serum. PNH RBCs provided by Dr. Jaroslaw Maciejewski (CCF IRB 5024)