A PHASE 1 MULTIPLE-DOSE CLINICAL STUDY OF RA101495, A SUBCUTANEOUSLY ADMINISTERED SYNTHETIC MACROCYCLIC PEPTIDE INHIBITOR OF COMPLEMENT C5 FOR TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Jeffrey Johnston[1], Alonso Ricardo[1], Michelle Arata[1], Jason Lickliter[2], Steven DeMarco[1], Richard Fahrner[1], Robert Hammer[1], Beth Newstat[1], Debasish Roychowdhury[1], Sylvia Tobé[1], Debra Winslow[1] and Douglas Treco[1]. [1]Ra Pharmaceuticals Inc., Cambridge, United States; [2]Nucleus Network, Melbourne, Australia; Contact: Jeffrey Johnston – jjohnston@rapharma.com

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, clonal hematopoietic stem cell disorder caused by a deficiency in glycosylphosphatidylinositol (GPI)-linked proteins on cell surfaces. Patients with mutations in the phosphatidylinositol glycan class A gene are unable to produce functional, protective, GPI-linked proteins, resulting in the accumulation of specific complement proteins on the surface of red blood cells (RBCs) and subsequent RBC lysis by the membrane attack complex (MAC). Inhibition of complement activation at the level of complement C5 is a clinically validated approach for the treatment of PNH. RA101495, a synthetic macrocyclic peptide, binds to C5 at a unique site not targeted by currently available therapies, and allosterically inhibits C5 cleavage into C5a and C5b, preventing production of a key component of the MAC. RA101495 also inhibits the assembly of MAC by blocking the interaction between C5b and C6.

Objectives

- To evaluate the safety and tolerability of multiple daily doses of RA101495 administered to healthy adult volunteers by subcutaneous (SC) injections
- To characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of multiple doses of RA101495 administered to healthy adult volunteers by SC injections

Methods

- Design: Phase 1, randomized, double-blind, placebo-controlled, multiple-dose study of safety, PK, and PD
- Aim: demonstrate that daily dosing for 7 days achieves ≥90% sustained inhibition of hemolysis
- N = 6 (4 on RA101495 and 2 on placebo)
- Dose: 0.2 mg/kg administered SC once daily x 7 days
- *Neisseria meningitides* prophylaxis (ciprofloxacin x 7 days and vaccination)
- 8 days inpatient and 4 weeks outpatient monitoring
- Blood samples were taken at pre-dose, and post-dose at 3 hr and 6 hr on each dosing day and at each follow-up visit for PK and PD assessments
- LC/HRMS for RA101495 plasma concentrations to assess PK
- *Ex vivo* antibody-sensitized sheep erythrocyte (sRBC) hemolysis assays to assess classical pathway of complement
- Wieslab ELISA to assess the alternative pathway of complement
- Phase 1 Clinical Pharmacology Unit, Nucleus Network (Melbourne, Australia)

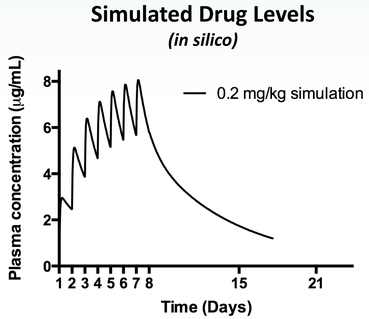
Results
Demographics

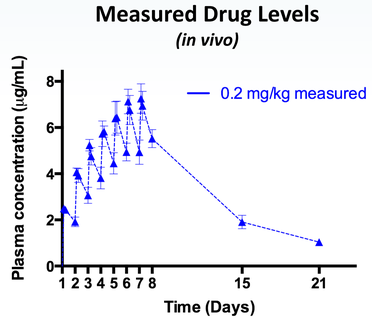
	Placebo n=2	RA101495 n=4
Male : Female	0 : 2	1 : 3
Mean Age, years (min, max)	27 (25, 29)	24 (22, 26)
Mean BMI*, kg/m^2	21	23
White : Asian	2 : 0	3 : 1

*BMI = Body Mass Index

Pharmacokinetics

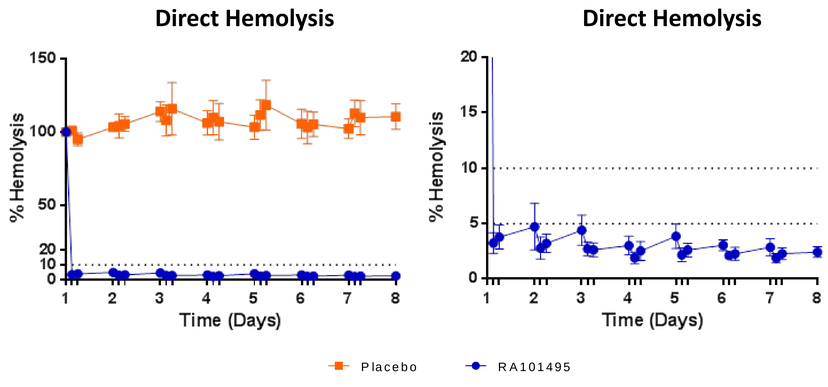
- All subjects achieved drug levels consistent with predicted values from *in silico* PK model generated using data from non-human primate (NHP) studies and single dose human study
- Consistent plasma levels across all subjects with very low variability in exposure
- Peak drug levels observed at 3h post-dosing in all subjects
- At a 0.2 mg/kg dose level, RA101495 concentrations in plasma are expected to reach steady-state by Day 11 (without a loading dose)





Pharmacodynamics

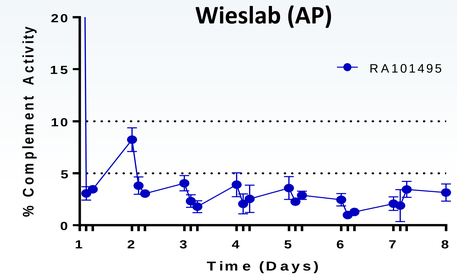
- Inhibition of hemolysis was rapid and sustained at ≥95% across the dosing period in all subjects
- Hemolysis at Day 8 (24h after receiving the last dose) was observed to be ≤3% in all subjects
- Hemolysis returned to pre-dose levels within two weeks following the last dose



Multiple Dose Study % Hemolysis (sRBC Lysis)		Day 1: 3 hr	Day 2	Day 8
0.2 mg/kg n=4	Min % (SEM)	1.9 (0.1)	2.4 (0.1)	1.5 (0.3)
	Mean % (SEM)	3.2 (0.9)	4.7 (2.1)	2.4 (0.5)

Pharmacodynamics (Cont.)

- Suppression of complement activity was rapid, complete and sustained across the dosing period in all subjects
- Complement activity at Day 8 (24h after last dose) was observed to be ≤5% in all subjects
- Complement activity returned to pre-dose levels within two weeks following the last dose



Multiple Dose Study % Complement Activity		Day 1: 3 hr	Day 2	Day 8
0.2 mg/kg n=4	Min % (SEM)	1.8 (0.8)	6.9 (0.3)	2.1 (0.1)
	Mean % (SEM)	3.1 (0.6)	8.2 (1.1)	3.1 (0.8)

Safety and Tolerability

- Repeat dosing of RA101495 was safe and well-tolerated in healthy volunteers
- Injection site erythema (ISE) was observed in 3 of 6 subjects (all 3 in the RA101495 dose group; observed after 1/7 injections in 2 subjects, and after 4/7 injections in a 3rd subject)
- All ISEs were mild (grade 1) with no pain, induration, tenderness or swelling and all resolved spontaneously
- No clinically significant changes were observed in vital signs, clinical laboratory parameters (hematology, blood chemistry, coagulation, and urinalysis), physical exams and ECGs

Related TEAE†s	All N=6	Placebo n=2	RA101495 n=4
Any related TEAE by subject	**6**	**2**	**4**
Injection site erythema	3	0	3
Headache	2	1	1
Lightheadedness	1	0	1
Rash	1	0	1
Injection site stinging	1	1	0
URI*	1	1	0

†TEAE = Treatment Emergent Adverse Event
*URI = Upper Respiratory Infection

Conclusions

- RA101495 was safe and well tolerated over 7 daily doses at 0.2 mg/kg in healthy volunteers Inhibition of hemolysis was rapid and sustained at ≥95% across the dosing period in all subjects
- The findings from this Phase 1 study confirm that daily dosing with RA101495 (0.2 mg/kg) results in full suppression of complement activity and complete inhibition of hemolysis
- RA101495 displayed consistent and predictable pharmacokinetics which were highly correlated with the pharmacodynamic effect (inhibition of hemolysis and complement activity)
- RA101495 is a potent inhibitor of complement component C5 with the potential to be used as a therapeutic agent in multiple complement disorders
- A Phase 2 trial in PNH patients (both eculizumab-naïve and eculizumab-treated) is planned to begin in 2H2016
- The investigational product will be provided in a convenient auto-injector device for daily self-administration