#P632

A PHASE 1 SINGLE-ASCENDING-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 single-escalating doses of RA101495 administered to healthy adult volunteers by subcutaneous (SC) injection
- To characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of single-escalating doses of RA101495 administered to healthy adult volunteers by SC injection

Methods

- Design: Phase 1, randomized, double-blind, placebo-controlled, single-escalating-dose study of RA101495 safety, PK, and PD
- Aim: Demonstrate single dose that achieves ≥90% inhibition of hemolysis for >24 hours
- N = 22 (RA101495: 2 in Cohort 1, 4 in Cohorts 2-4; Placebo: 2 per cohort)
- Doses: 0.05 mg/kg (cohort 1), 0.1 mg/kg (cohort 2), 0.2 mg/kg (cohort 3), and 0.4 mg/kg (cohort 4) administered SC; staggered dosing with 2 sentinel patients per cohorts; safety review prior to escalation to next cohort
- *Neisseria meningitides* prophylaxis (ciprofloxacin x 3 days, plus vaccination for Cohort 4)
- 3 days inpatient and 4 weeks outpatient monitoring
- Blood samples were taken at pre-dose, and post-dose at 15 min, 1 hr, 3 hr, 6 hr, 12 hr, 24 hr and 48 hr in clinic 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 PD
  - Direct hemolysis (classical pathway)
  - %CH50 (classical pathway)
- Wieslab ELISA to assess the alternative pathway of complement
- Phase 1 Clinical Pharmacology Unit, Nucleus Network (Melbourne, Australia)

Results

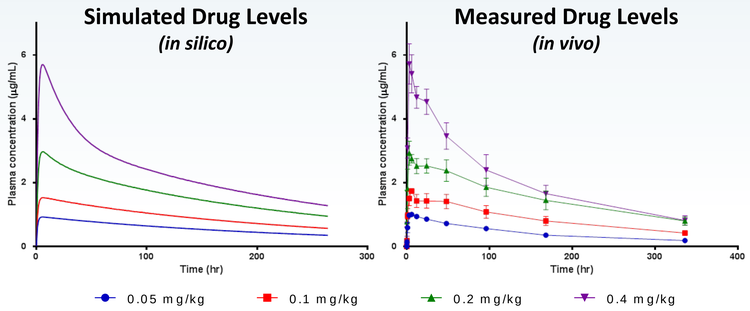
Demographics

	Placebo n=8	0.05 mg/kg n=2	0.1 mg/kg n=4	0.2 mg/kg n=4	0.4 mg/kg n=4	All N=22
Male : Female	2 : 6	0 : 2	0 : 4	0 : 4	1 : 3	3 : 19
Mean Age, years (min, max)	39 (20, 59)	23 (22, 23)	27 (20, 37)	34 (22, 65)	32 (21, 58)	33 (20, 65)
Mean BMI*, kg/m^2	24	20	21	26	27	24
White : Black : Asian	7 : 1 : 0	2 : 0 : 0	2 : 1 : 1	3 : 0 : 1	4 : 0 : 0	18 : 2 : 2

*BMI = Body Mass Index

Pharmacokinetics

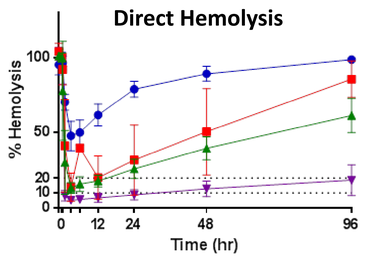
- All cohorts achieved C_{max} levels consistent with predicted values from *in silico* PK model
- Linear relationship observed between C_{max} and dose level; confirmed dose-dependent exposure
- Approximate $t_{1/2}$ across all cohorts is 7 days



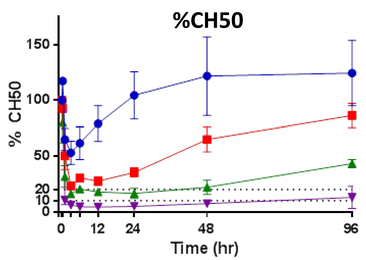
PK Parameter	0.05 mg/kg n=2	0.1 mg/kg n=4	0.2 mg/kg n=4	0.4 mg/kg n=4
Mean C_{max} (ng/mL) (SD)	1010 (14)	1550 (198)	2970 (318)	5873 (441)
Mean AUC $_{(0\text{-last})}$ (hr*ng/mL) x10^3 (SD)	179.8 (3.2)	375.4 (47.5)	655.1 (113.7)	822.6 (120.7)
Mean $t_{1/2}$ (hr) (SD)	163.5 (10.9)	185.4(6.4)	172.0 (24.8)	155.6 (14.3)

Pharmacodynamics

- RA101495 exhibited a rapid dose-dependent inhibition of hemolysis (direct hemolysis and %CH50) and suppression of complement activity (Wieslab) in all subjects after a single dose
- A maximum PD effect was observed approximately 3h after dosing
- A single dose of RA101495 at 0.4 mg/kg resulted in ≥90% suppression of hemolysis for at least 4 days
- Sustained inhibition of hemolysis at highest dose suggests possibility for weekly dosing

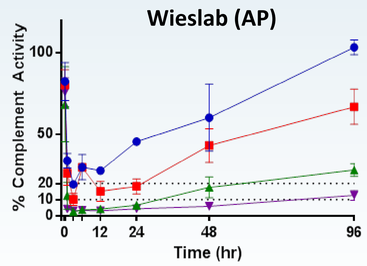


Single Ascending Dose Study % Hemolysis (sRBC Lysis)		0.2 mg/kg n=4	0.4 mg/kg n=4
3 Hours	Min % (SEM)	10.0 (0.3)	2.5 (0.2)
	Mean % (SEM)	13.2 (1.8)	5.1 (1.2)
24 Hours	Min % (SEM)	19.8 (0.7)	5.0 (0.3)
	Mean % (SEM)	26.1 (3.5)	8.8 (1.8)



Single Ascending Dose Study % CH50 (sRBC Lysis)		0.2 mg/kg n=4	0.4 mg/kg n=4
3 Hours	Min % (SEM)	10.3 (5.5)	1.3 (0.1)
	Mean % (SEM)	16.1 (2.1)	6.0 (1.8)
24 Hours	Min % (SEM)	4.1 (5.2)	0.4 (1.3)
	Mean % (SEM)	16.6 (4.6)	4.9 (2.7)

Pharmacodynamics (Cont.)



Single Ascending Dose Study % Complement Activity		0.2 mg/kg n=4	0.4 mg/kg n=4
3 Hours	Min % (SEM)	1.3 (0.2)	1.4 (0.2)
	Mean % (SEM)	2.6 (0.6)	3.2 (0.8)
24 Hours	Min % (SEM)	4.3 (0.2)	3.4 (0.4)
	Mean % (SEM)	6.6 (1.2)	4.5 (0.6)

Safety and Tolerability

- Single SC doses of RA101495 were safe and well tolerated in healthy volunteers
- Injection site erythema (ISE) was observed in 3 subjects at the highest dose and was mild (grade 1) with no pain, induration, tenderness or swelling and resolved spontaneously within 2-5 hours post-injection
- 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=22	Placebo n=8	Total RA101495	0.05 mg/kg n=2	0.1 mg/kg n=4	0.2 mg/kg n=4	0.4 mg/kg n=4
Subjects with Any Related TEAE	**8**	**3**	**5**	**1**	**0**	**0**	**4**
ISE	3	0	3	0	0	0	3
URI†	1	0	1	1	0	0	0
Fatigue	1	0	1	0	0	0	1
Headache	2	1	1	0	0	0	1
Diarrhea	1	1	0	0	0	0	0
Myalgia	1	1	0	0	0	0	0

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

Conclusions

- RA101495 was safe and well tolerated in a Phase 1 single ascending dose study in healthy volunteers
- RA101495 displayed dose-dependent exposure and predictable pharmacokinetics demonstrating strong correlation with the pharmacodynamic effect
- RA101495 exhibited a rapid dose-dependent inhibition of hemolysis (direct hemolysis and %CH50) and suppression of complement activity (Wieslab) in all subjects after a single dose
- The results from this Phase 1 study combined with *in silico* modeling studies suggest that daily dosing with RA101495 (0.2 mg/kg) should result in full suppression of complement activity and complete inhibition of hemolysis
- RA101495 is being developed for the treatment of PNH as a daily, self-administered product
- Phase 2 studies in PNH patients expected to begin in 2H 2016

Preliminary data from a RA101495 repeat dosing study in healthy volunteers (0.2 mg/kg) support the use of this macrocyclic peptide as a treatment to achieve clinically meaningful suppression of complement activity as measured by inhibition of hemolysis (see poster LB2249)