Ra Pharma

Next Generation Therapeutics for Disorders of Complement Regulation

January 2017
This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding the safety, efficacy and regulatory and clinical progress of our product candidates, including RA101495. All such forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include the risks that Ra Pharma’s product candidates, including RA101495, will not successfully be developed or commercialized; as well as the other factors discussed in the “Risk Factors” and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections in Ra Pharma’s Registration Statement on Form S-1 (File No. 333-214242), as amended, which is on file with the Securities and Exchange Commission and was declared effective on October 25, 2016, as well as other risks detailed in Ra Pharma’s subsequent filings with the Securities and Exchange Commission. There can be no assurance that the actual results or developments anticipated by Ra Pharma will be realized or, even if substantially realized, that they will have the expected consequences to, or effects on, Ra Pharma. All information in this press release is as of the date of the release, and Ra Pharma undertakes no duty to update this information unless required by law.
Overview

- Focused on disorders of complement regulation
  - Addressing orphan hematologic, renal, neurologic, ocular and autoimmune indications

- **Lead Clinical Program: RA101495 for paroxysmal nocturnal hemoglobinuria (PNH)**
  - Potent, synthetic macrocyclic peptide inhibitor of complement C5
  - Distinct binding site on C5 vs. eculizumab
  - Convenient self-administered subcutaneous dosing
  - Phase 2 ready: Completed Phase 1 safety, PK, and PD study in healthy volunteers
    - Rapid, sustained, near complete suppression of hemolysis and complement activity
  - Received orphan drug designation from European Medicines Authority (EMA)

- **Powerful proprietary drug discovery engine**
  - Basis for a portfolio of specific and stable peptide drugs targeting C5 and other complement pathway factors
  - Enables application to diseases with high unmet medical need and/or for which only mAbs have previously been successful

- **Collaboration with Merck validates the platform**
  - Delivered orally-available peptides for a non-complement cardiovascular target with a large market opportunity

- **$105.4 million gross proceeds raised in October 2016 initial public offering**
<table>
<thead>
<tr>
<th>Pipeline</th>
</tr>
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<tbody>
<tr>
<td><strong>C5 Inhibition</strong></td>
</tr>
<tr>
<td>RA101495  (PNH; SC)</td>
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<tr>
<td>RA101495  (Refractory Myasthenia Gravis; SC)</td>
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<td>RA101495  (Lupus Nephritis; SC)</td>
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<tr>
<td>Oral Small Molecule Inhibitor  (PNH, rMG, LN, CNS diseases)</td>
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<tr>
<td><strong>Factor D Inhibition</strong></td>
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<tr>
<td>Dry AMD/GA (intravit.), orphan renal diseases, (SC)</td>
</tr>
<tr>
<td><strong>C1s Inhibition</strong></td>
</tr>
<tr>
<td>Autoimmune/CNS Diseases</td>
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</tbody>
</table>
| **Partnered Program**  
(Non-Complement target) |
| Oral macrocyclic peptide  
(Cardiovascular target with a large market opportunity) |

(1) We intend to leverage our work in PNH, including CMC, and preclinical data packages, to advance RA101495 for rMG and LN.
RA101495:
- Blocks C5 cleavage and production of C5a and C5b—Same outcome as eculizumab supports similar clinical efficacy
- Blocks interaction of C5b with C6 and MAC formation—Unique property
  - May be beneficial in hypercoagulative and inflammatory states, where thrombin and other proteases can cleave C5
Our Extreme Diversity Platform
mRNA Display Platform:
A New Approach to Building Drug-like Peptide Libraries

Translation with natural and non-natural amino acids and cyclization to increase stability, potency, cell permeability, and bioavailability

Rapid lead generation capabilities

Utility
- Filling unmet needs associated with current monoclonal antibody, biologic, and peptide therapies
- Ability to distinguish between closely related targets
- Modulators of the undruggable proteome: Disrupt intracellular protein-protein interactions

1. Translation of mRNA to peptides to create peptide-mRNA fusion
2. Cyclize to create macrocyclic peptides, convert mRNA to cDNA
3. Affinity selection to immobilized target
4. Copy DNA into mRNA and attach puromycin
5. PCR amplify cDNA to produce large quantities of corresponding DNA
6. Sequence DNA and synthesize peptide candidates
7. Optimize Hits

Large and diverse library of macrocycle peptide-cDNA fusions
DNA corresponding to selected peptides
Candidate Peptides
Drug Lead
RA101495 in Paroxysmal Nocturnal Hemoglobinuria (PNH)
RA101495:
Paroxysmal Nocturnal Hemoglobinuria (PNH)

- Rare, chronic, *acquired* hematologic syndrome where red blood cells (RBCs) are destroyed by the complement system
  - ~16,000 patients worldwide
- Results in death of 35% of patients within 5 years and 50% within 10 years of diagnosis
  - Most common cause of mortality is thrombosis
- Only 1 approved therapy: Anti-Complement C5 monoclonal antibody [eculizumab (Soliris®); Alexion]
  - Biweekly IV infusion
  - Approved for PNH and atypical hemolytic uremic syndrome (aHUS)
  - 2016 revenues (est.): $3.1B
- Straightforward clinical endpoints
  - Markers of hemolysis, hemoglobin levels, transfusion requirements
  - Strong correlation between level of hemolysis suppression and clinical benefit
RA101495: Binds a Site on C5 That is Distinct From Eculizumab

- **Distinct from eculizumab binding site**—allows treatment of patients with R885H/C mutations
- Peptides targeting novel druggable sites provide a toolkit for developing true small molecule inhibitors of C5
RA101495: Clinical Development Overview

- Phase 1, placebo-controlled, single-ascending dose and multiple dose study in healthy volunteers completed 2Q2016
  - Highly predictable PK after single and multiple SC injections, with dose dependent exposure
  - Suppression of (ex vivo) hemolysis and complement activity was rapid, near-complete and sustained
  - Single and repeat doses of RA101495 were well tolerated in healthy volunteers

- Planned open-label Phase 2 global studies in up to 28 patients
  - Naïve patients, patients who are currently treated with eculizumab, and patients who respond inadequately to eculizumab
  - Plan to initiate in 1Q2017

- Plan to pursue other indications, Refractory Myasthenia Gravis (rMG) and Lupus Nephritis (LN) in parallel
Randomized, placebo-controlled, double-blind, safety and dose finding study in healthy volunteers (n=22)

Ciprofloxacin prophylaxis

Cipro + Neisseria vaccination

Cohort 1
n=2 RA101495
n=2 Placebo

Cohort 2
n=4 RA101495
n=2 Placebo

Cohort 3
n=4 RA101495
n=2 Placebo

Cohort 4
n=4 RA101495
n=2 Placebo

48 hours in-patient monitoring

0.05mg/kg

0.1mg/kg

0.2mg/kg

0.4mg/kg

4 week follow up to assess safety and collect PK/PD data

One center: Australia

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RA101495: Pharmacokinetics
Predictable, Dose-Dependent Exposure After Single SC Injections

- Linear relationship observed between $C_{\text{max}}$ and dose level
- Approximate terminal half-life across all cohorts is 7 days
- RA101495 Pharmacokinetics consistent with predicted values from \textit{in silico} PK model generated using data from non-human primate (NHP) studies

n=2 (0.05 mg/kg) or 4 (0.1-0.4 mg/kg) per group
After a single dose, RA101495 exhibited a rapid dose-dependent inhibition of ex vivo hemolysis and suppression of complement activity in all subjects.

Maximum PD effect observed ~3h to ~6h after dosing.

A single dose of RA101495 at 0.4 mg/kg resulted in ≥90% suppression of hemolysis for at least 4 days in some subjects.

Sustained inhibition of hemolysis at highest dose suggests possibility of less frequent dosing.

n=2 (0.05 mg/kg) or 4 (0.1-0.4 mg/kg) per group.
Randomized, double-blind, placebo-controlled, multiple-dose study of safety, PK, and PD in healthy volunteers

Randomize

- Ciprofloxacin prophylaxis + *Neisseria* vaccination
  - n=6
  - Placebo n=2
  - 0.2 mg/kg n=4

7 daily doses (8 days in-patient monitoring)

One center: Australia

4 week follow up to assess safety and collect PK/PD data
RA101495:
PK Model Predicts Plasma Drug Levels In Phase 1 Multiple-Dose Cohort

- Modeling of non-human primates (NHP) and human (healthy volunteer) PK data accurately predicted observed results
- Consistent pharmacokinetics across all subjects with minimal variability in exposure
- 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)

Model vs. Actual Mean Plasma RA101495 Levels
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.
RA101495 Protects Against Complement-Mediated Hemolysis of Type III PNH Erythrocytes

Dose response

Drug concentration

No drug

RA101495

No drug

Eculizumab

Approx. 1 μM 101495 or Ecu (Note: Ecu is bivalent)

Flow cytometry

Serum*

Serum + HCl

Serum + HCl + Eculizumab (1 μM)

Serum + HCl + RA101495 (1.2 μM)

Type III

Type I+II

*18h incubation of PNH RBCs with 50% acidified serum. PNH RBCs provided by Dr. Jaroslaw Maciejewski
RA101495 is a potent inhibitor of complement C5

Single and repeat SC doses of RA101495 were well tolerated in healthy volunteers

RA101495 displayed dose-dependent exposure (SAD) and consistent and predictable pharmacokinetics, which were highly correlated with its pharmacodynamic effect (inhibition of hemolysis in *ex vivo* RBC lysis assay)

The findings from single- and multi-dose administration studies confirm that daily dosing with RA101495 (0.2 mg/kg) results in near-complete suppression of complement activity and hemolysis

Phase 2 trial in PNH patients (eculizumab-naïve and eculizumab-treated) is planned to begin in 1Q2017

- RA101495 expected to be provided in a convenient device for daily self-administration

Received a positive opinion for orphan drug designation from EMA COMP for RA101495 for the treatment of PNH
RA101495: PNH
Planned Phase 2 Design

- **Goal:** To evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of RA101495 in subjects with PNH

- **Design:** Open-label (12 weeks) with long-term extension

- **Global Program addressing 3 PNH populations**
  - Eculizumab Naïve
  - Eculizumab Switch
  - Eculizumab Inadequate Responders

- **Primary Efficacy Endpoint:** Change in Lactate Dehydrogenase (LDH)
RA101495: Planned Phase 2 Design

**Cohort A (naïve)**
- n=8-12
- 0.1mg/kg, q.d.
- 0.3mg/kg Loading Dose
- 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
- 0.1mg/kg, q.d.
- 0.3mg/kg Loading Dose
- Review of safety & efficacy
- Evaluation period for primary efficacy endpoint (change in LDH from baseline to mean of W6-12)

**Inadequate Responders**
- (LDH > 1.5 x ULN)
- n=6-8
- 0.1mg/kg, q.d.
- 0.3mg/kg Loading Dose
- Review of safety & efficacy
- Evaluation period for primary efficacy endpoint (change in LDH from baseline to mean of W6-12)
Daily Dosing Allows Maintenance of a Stable Drug Level as Compared to Bolus, Biweekly Dosing

Daily administration greatly reduces risk of drop in plasma drug levels below minimally efficacious level.
RA101495:
Potential Advantages of a Macrocyclic Peptide Inhibitor of C5

- **Highly predictable PK, robust PD effects**
  - Linear relationship between dose and $C_{\text{max}}$
  - Observed from Phase 1 data to maintain $\geq 97\%$ hemolysis suppression at 24 hours after last dose
  - Weekly dosing considered feasible

- **Improved control of hemolysis (Daily vs. high-dose biweekly IV infusion)**
  - Sustained suppression: dosing designed for continuous suppression (vs. bolus IV and decay over 2 weeks)

- **Subcutaneous route of administration (vs. IV)**
  - Improved quality of life (Inconvenience and lack of freedom associated with IV infusion)
  - Reduced complications of IV infusion (Infection, venous access, thrombosis, comfort of ports)
  - Reduced treatment costs and reduced time/economic losses associated with home/clinic infusion

- **Expanded target population (Distinct binding site vs. eculizumab)**
  - Treatment of patients with R885H/C mutations

- **Synthetic product (non-recombinant)**
  - Non-biologic, essentially no risk of contamination by viruses and animal cell products
  - Treat patients with hypersensitivity to CHO-derived products

- **Novel mechanistic feature (vs. eculizumab)**
  - Potential to reduce complement damage mediated by other pathways
## RA101495: A Well-Differentiated Profile For Treating PNH

<table>
<thead>
<tr>
<th>RA101495</th>
<th>ALN-CC5</th>
<th>Coversin</th>
<th>ALXN1210</th>
<th>LFG316</th>
<th>RO7112689</th>
<th>APL-2</th>
<th>ACH-4471</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td>Cyclic peptide</td>
<td>RNAi</td>
<td>Tick saliva protein</td>
<td>mAb</td>
<td>mAb</td>
<td>mAb</td>
<td>Cyclic peptide</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>C5</td>
<td>Liver C5 mRNA</td>
<td>C5</td>
<td>C5</td>
<td>C5</td>
<td>C5</td>
<td>C3</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>IV, SC</td>
<td>IV</td>
<td>IV, SC</td>
<td>SC</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Daily, (Weekly)</td>
<td>Weekly-monthly</td>
<td>2x daily</td>
<td>Every 8-weeks</td>
<td>Biweekly/monthly</td>
<td>Unknown</td>
<td>Daily</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td>Ph2</td>
<td>Ph2</td>
<td>Ph3</td>
<td>Ph2</td>
<td>Ph1/2</td>
<td>Ph1</td>
<td>Ph1</td>
</tr>
<tr>
<td><strong>R885H/C Mutations</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Impact</strong></td>
<td>Rapidly and potently inhibits hemolysis</td>
<td>Not adequate for monotherapy</td>
<td>Insufficient inhibition from targeting liver C5 only</td>
<td>Extremely high doses</td>
<td>Chugai sweeping antibody technology</td>
<td>Not adequate for monotherapy</td>
<td>Significant LFT liability in Ph1</td>
</tr>
<tr>
<td></td>
<td>Convenient dosing</td>
<td>Short half-life</td>
<td>Immunogenicity</td>
<td>No safety margin for missed doses</td>
<td>Potential Saturation of FcRn</td>
<td>Increased risk of infection</td>
<td>Increased risks of infection and breakthrough hemolysis</td>
</tr>
<tr>
<td></td>
<td>Favorable PK</td>
<td>No supportive data from Ph2</td>
<td></td>
<td></td>
<td></td>
<td>Very high doses</td>
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**Announced biosimilar program: Amgen**
Complement Regulation Pipeline
Building a Complement Inhibitor Franchise

- Technology enables development of a portfolio of C5 inhibitor candidates suitable for chronic or acute indications
  - Can vary PK properties and route of administration
  - Allows different pricing structures for different indications
- Life cycle extension plan for C5 inhibitors
  - Weekly (depot) formulation
  - Druggability of RA101495 binding site has been used to identify true small molecule inhibitors of C5
- Leverage CMC and preclinical data on RA101495 to efficiently pursue other indications in parallel

**Refractory Myasthenia Gravis (rMG)**
- rMG affects approximately 9,000 patients in the United States
- Current therapies do not target injury caused by complement attack
- Inhibiting terminal complement activity may block complement-mediated damage

**Lupus Nephritis (LN)**
- LN affects approximately 63,000 patients in the United States
- Approximately 10%-15% will develop end-stage renal disease, requiring a kidney transplant or initiation of dialysis
- Binding C5 may prevent progression of kidney disease in LN by blocking complement-mediated damage to kidney cells

- Applying mRNA Display platform to other targets (Factor D, C1s)
  - Dry AMD/GA, orphan renal diseases (DDD and C3GN), autoimmune/CNS diseases
Next Generation of C5 Inhibitors: Orally Bioavailable Small Molecules

- Series of orally bioavailable (%F=30) small molecules that bind C5, inhibit its cleavage/activation ($IC_{50}$ 14 nM in 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
Factor D (FD) is a critical mediator of alternative pathway activation
Cleaves Factor B bound to C3b, generating C3 convertase (C3bBb)

Potential indications
- Dense deposit disease/Membranoproliferative Glomerulonephritis type II/C3 Glomerulopathy (High priority)
  - Uncontrolled activation of alternative pathway results in glomerular C3 deposition
  - Mutations/polymorphisms in complement genes associated with increased risk
- Dry age-related Macular Degeneration (High priority)
  - Polymorphism in complement regulatory factor H is risk factor for AMD\(^1\)
  - Positive Ph 2 data in geographic atrophy with anti-Factor D (Lampalizumab, Roche)
- Extravascular hemolysis in PNH patients treated with C5 inhibitor (Lower priority)
  - Reduce C3 fragment coating on PNH RBCs and subsequent spleen phagocytosis (extravascular hemolysis, EVH)
  - Potential for increased risk of infection may limit investigator interest

Factor D: Developing Multiple Molecules for Two Potential Value Streams

Highly potent inhibitors (low nanomolar)

Physical Properties
Solubility and Stability (PBS, Plasma, and Vitreous)
Log D etc.

In vitro DMPK
Microsomes, retinal pigmented epithelium stability,
CYP profile (including retinal CYPs)

Intravitreal (Dry AMD)
Low plasma stability
Lipophilic
Vitreal solubility
Microsomal and RPE stability

Systemic/SubQ (DDD/C3GN)
High plasma stability
Selective Inhibition of the Classical Pathway: C1s Macrocycle Project

- Multiple approaches to inhibition of C1 complex

- **C1q has an emerging number of non-complement functions**
  - Clearance of apoptotic cells and immunogenic debris
  - Tolerance induction in dendritic cells
  - Anti-proliferative effect on T-Cells and inhibition of B-cell signaling

- Ra macrocycle selections have targeted C1s specific and dual C1s/C1r binding peptides to potentially avoid broad non-complement effects of C1q
  - Preclinical evaluation underway

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### Potential Indications and Competition

<table>
<thead>
<tr>
<th>Indication</th>
<th>Incidence</th>
<th>Competition/Status</th>
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<tbody>
<tr>
<td>Cold agglutinin disease</td>
<td>~1 in 80,000</td>
<td>Anti-C1s TNT-009 (TrueNorth) / Ph1</td>
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<tr>
<td></td>
<td></td>
<td>Soliris (Alexion) / Ph2</td>
</tr>
<tr>
<td>Warm autoimmune hemolytic anemia</td>
<td>~1 in 100,000</td>
<td>Anti-C1s TNT-009 (TrueNorth) / Ph1</td>
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<td></td>
<td></td>
<td>Fostamatinib (Rigel)-oral Syk inhibitor / Ph2</td>
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<tr>
<td></td>
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<td>Rituximab (Roche) / Ph3</td>
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<tr>
<td>Neurodegenerative disease (AD, HD, ALS, GBS)</td>
<td>e.g. AD ~5.4 million in US as of 2015</td>
<td>Anti-C1q (Annexon) / Pre-clinical</td>
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</tbody>
</table>
Leadership Team

Doug Treco, PhD
Co-Founder, President and CEO

Ramin Farzaneh-Far, MD
Chief Medical Officer

David Lubner
EVP, Chief Financial Officer

Simon Read, PhD
Chief Scientific Officer

Alonso Ricardo, PhD
SVP, Research and Development

Jack W. Szostak, PhD
Co-Founder
Financial Summary

- $31.2 million in cash and cash equivalents as of September 30, 2016

- $105.4 million gross proceeds raised in October, 2016 initial public offering
  - $95.7 million net proceeds

- Collaboration with Merck represents opportunity for additional milestone and royalty payments
  - Delivered orally-available cyclic peptides for a non-complement cardiovascular target with a large market opportunity, now in development at Merck
  - $17.5M received to date; with additional potential milestones of up to $61.5M and royalties
Upcoming Milestones

- Initiate Phase 2 global studies in PNH 1Q 2017
- Data readout of Phase 2 studies in PNH 2H 2017
- Initiate Phase 2 study in rMG 2H 2017
- Initiate Phase 1b in LN 2H 2017
Investment Highlights

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jrobinson@rapharma.com