Introduction to Ra Pharma & the Potential of Zilucoplan for the Treatment of IMNM

Webinar, November 6, 2019

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Forward-Looking Statements

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, regulatory and clinical progress, and therapeutic potential of the product candidates of Ra Pharmaceuticals, Inc. ("Ra Pharma” or “we”), including, zilucoplan, the poly(D,L-lactic-co-glycolic acid) (PLGA) and FluidCrystal® (FC) extended release (XR) formulations of zilucoplan, and an oral small molecule inhibitor of C5, plans and timing for the presentation of clinical data, expectations surrounding the trial design, timeline, and enrollment of Ra Pharma’s ongoing and planned clinical programs, including a Phase 3 clinical program evaluating zilucoplan for the treatment of generalized myasthenia gravis (gMG), a Phase 2 trial of zilucoplan for the treatment of immune-mediated necrotizing myopathy (IMNM), and the Healey Center-led ALS platform trial, our market opportunities, and management’s estimates about the potential size and characteristics for the patient populations that Ra Pharma’s product candidates are targeting. Zilucoplan is an investigational drug, and the claims, or indications, discussed are not yet approved by the FDA. 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 zilucoplan, the PLGA and FC XR formulations of zilucoplan, and an oral small molecule inhibitor of C5, will not successfully be developed or commercialized, risks related to fluctuations in Ra Pharma’s stock price, as well as the other factors discussed in the “Risk Factors” section in Ra Pharma’s most recently filed Annual Report on Form 10-K, 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. Except as noted, all information in this presentation is as of November 6, 2019, and Ra Pharma undertakes no duty to update this information unless required by law.
A Brief History
Incorporated in 2008
Located in Cambridge, MA
Founded by Doug Treco (CEO) and Jack Szostak (MGH, 2009 Nobel Laureate)
Currently ~75 employees
Focused on rare diseases mediated by the complement system

Leading the Field of Complement Biology to Bring Innovative and Accessible Therapies to Patients with Rare Diseases
### Pipeline Programs

<table>
<thead>
<tr>
<th>C5 Inhibition</th>
<th>DISCOVERY/ PRE-CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
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<tbody>
<tr>
<td>Zilucoplan (gMG)</td>
<td>Phase 3 RAISE trial ongoing</td>
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<td>Zilucoplan (IMNM)</td>
<td>Phase 2 trial planned</td>
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<td>Zilucoplan (ALS)</td>
<td>Phase 2/3 HEALEY ALS Platform Trial planned</td>
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<td>Zilucoplan (renal disorders)</td>
<td>Phase 1b trial complete</td>
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<td>Zilucoplan Extended Release (XR)</td>
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<td>Oral Small Molecule Inhibitor</td>
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<td>Factor D Inhibition</td>
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<td>Orphan Renal Diseases (SC)</td>
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<td>Other Complement Inhibitors</td>
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<tr>
<td>Renal/Autoimmune/CNS Diseases</td>
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<td>Partnered Program</td>
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<tr>
<td>(Non-Complement Target)</td>
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<td>Oral Macroyclic Peptide</td>
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<td>Cardiovascular target with a large market opportunity</td>
<td>Phase 1 trial ongoing</td>
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</table>

**Phase 1 trials**
- Phase 3 RAISE ongoing
- Phase 2 trial planned
- Phase 2/3 HEALEY ALS Platform Trial
- Phase 1b trial complete
- Phase 1 trial ongoing
Zilucoplan
& Complement Inhibition
Zilucoplan: A Self-Administered, Subcutaneous, Macro cyclic Peptide Inhibitor of Complement C5

Multiple validated indications, pipeline-in-a-product potential

Alternative Pathway
Activated by non-self cells

Classical Pathway
Activated by antibody-antigen complexes

Lectin Pathway
Activated by pathogen surfaces

Factor D, Factor B
C3

Factor D, Factor B
C3

Eculizumab (IV)
Binds C5, blocks cleavage

Proinflammatory cytokine
C5a

C5

C1q – C1r – C1s

C5b

C5b6

15 amino-acid cyclic peptide inhibitor of C5

C7, C8, C9

Membrane attack complex (MAC)

Zilucoplan (SC)
Binds C5, blocks cleavage; Blocks MAC assembly

C1q – C1r – C1s

C5

C6

IMNM: Phase 2 planned
ALS: Platform trial planned
PNH: Phase 2 positive
Renal Disorders: Phase 1b positive

Multiple Indications

gMG: Phase 2 positive
Phase 3 ongoing

IMNM: Phase 2 planned

ALS: Platform trial planned

PNH: Phase 2 positive

Renal Disorders: Phase 1b positive

gMG – generalized myasthenia gravis; IMNM – immune-mediated necrotizing myopathy; ALS – amyotrophic lateral sclerosis; PNH – paroxysmal nocturnal hemoglobinuria
Designed for Everyday Control with Easy-to-Use Prefilled Syringe

- ✓ Short Injection
  ~5 Seconds

- ✓ BD UltraSafe™ PLUS
  Easy-to-use self-injection (used in approved products)

- ✓ Small Volume
  ~0.5 mL
  ~1/4 of a thimble

- ✓ Convenience & Privacy
  Privacy of self administration at home and freedom to travel

- ✓ Everyday Control
  Part of daily routine, like brushing your teeth or taking insulin injection

Zilucoplan
Phase 2 gMG
Top-line Results
Zilucoplan 0.3 mg/kg Achieved Rapid, Clinically Meaningful, Statistically Significant, and Sustained Reductions in QMG and MG-ADL

*1-sided analysis of covariance for LS mean change from baseline for 0.3 mg/kg arm vs. placebo; placebo patients re-baselined to zero upon completion of 12-week main study.
†2-sided t test for LS mean change from week 12 to week 24 for placebo patients crossing over to 0.3 mg/kg (n=7).
‡2-sided t test for LS mean change from week 0 to week 24 for 0.3 mg/kg arm.

CFB, change from baseline; LS, least squares; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis; SEM, standard error of the mean.
Zilucoplan 0.3 mg/kg Achieved Rapid, Clinically Meaningful, Statistically Significant, and Sustained Reductions in MG Composite and MGQoL15r

1-sided analysis of covariance for LS mean change from baseline for 0.3 mg/kg arm vs. placebo; placebo patients re-baselined to zero upon completion of 12-week main study.

2-sided t test for LS mean change from week 12 to week 24 for placebo patients crossing over to 0.3 mg/kg (n=7).

*1-sided test for LS mean change from week 0 to week 24 for 0.3 mg/kg arm.

CFB, change from baseline; LS, least squares; MGQoL15r, 15-item Myasthenia Gravis Quality-of-Life revised scale; SEM, standard error of the mean.
## Phase 2 Safety and Tolerability Profile Support Continued Development

<table>
<thead>
<tr>
<th>Patients Requiring Rescue with IVIG or PLEX</th>
<th>Placebo (n=15)</th>
<th>Zilucoplan 0.1 mg/kg (n=15)</th>
<th>Zilucoplan 0.3 mg/kg (n=14)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3 (20%)</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients with adverse events (AEs)</td>
<td>12</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Patients with related AEs</td>
<td>3</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Patients with serious AEs</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Patients with related serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients with most common related AEs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Injection site scab</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Contusion</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Patients with injection site reactions</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

- No meningococcal infections
- Profile consistent with Ph1 and Ph2 PNH studies
- All 44 subjects completed 12-week study; No early withdrawals
- 42/44 subjects (95%) entered long-term extension

No patients required rescue in 0.3 mg/kg zilucoplan arm
IMNM
& Complement Inhibition
Immune-Mediated Necrotizing Myopathy (IMNM): A Distinct Idiopathic Inflammatory Myopathy

**Diagnosis:**
Anti-SRP and anti-HMGCR IMNM can be diagnosed with commercially-available antibody tests.

**Prevalence:** ~21/Million²-¹⁰
- US: ~6,300 cases
- EU: ~6,500 cases
- Japan: ~2,500 cases

**Epidemiology:**
Age of onset, typically 40 to 60 years, predominantly affects females⁵-⁷

**Idiopathic Inflammatory Myopathies¹**
- Anti-synthetase syndrome
- Dermatomyositis
- Inclusion body myositis

- IMNM
  - Anti-SRP
  - Anti-HMGCR
  - Ab negative
  - ~70%
  - ~30%
IMNM: A Severe and Debilitating Disease of Muscle Necrosis

Severe necrotizing myopathy with prominent complement deposition

Severe proximal muscle weakness, especially in lower limbs

Markedly elevated serum CK

Muscle atrophy and fatty replacement

Dysphagia

Neck weakness

Myalgia

Anti-HMGCR subtype
Associated with statin use in approximately 75% of patients

Anti-SRP subtype
Associated with extra-muscular manifestations in approximately 10-20% of patients

Anti-SRP and Anti-HMGCR Antibodies Initiate Complement-Mediated Tissue Damage in IMNM

Anti-SRP or Anti-HMGCR–Mediated Complement Activation

Mature Complement Cascade

Healthy Muscle Tissue

C5a

C5

C5b

Formation of MAC on cells

Necrotic Muscle Tissue

Creatine kinase release

Muscle Cell

Anti-SRP or Anti-HMGCR binding
Complement Plays a Central Role in the Pathophysiology of IMNM

Strong deposition of C5b-9 (MAC) in muscle fibers and blood vessels of patients with IMNM¹

Muscle fibers
Muscle fibers
Capillaries

Phenotypic rescue of IMNM-induced muscle weakness in complement-deficient mice²

Muscle weakness in mice can be induced with sera from patients with IMNM²

Pathogenicity of patient serum is dependent on the presence of complement²

Current Treatment Paradigm for IMNM Is Non-Specific and Inadequate

There are currently no approved treatments for IMNM

Despite intense immunosuppression, ~52 - 66% of patients show progression and incomplete recovery at two years

Multiple specialties are involved in IMNM management


**1ST LINE**

**Anti-SRP Myopathy**
- **Corticosteroids**
  - Prednisone/prednisolone (oral)
  - or Methylprednisolone (IV)

**Anti-HMGCR Myopathy**
- **Corticosteroids**
  - Prednisone/prednisolone (oral)
  - or Methylprednisolone (IV)

**2ND/3RD LINE**

**Immunosuppressives**
- Methotrexate
- Azathioprine
- Mycophenolate mofetil

**Rituximab (IV)**

**IVIg**

**Diagnose/Refer**
- Rheumatologists
- Neurologists
- Neuromuscular Specialists

**Treat/Manage**
IMNM Phase 2 Study
**Phase 2 Clinical Trial Will Evaluate the Potential of Zilucoplan for the Treatment of IMNM**

Randomized, double-blind, placebo-controlled, multi-center study, followed by an open-label long-term extension

**Broad Patient Population**
- Clinical diagnosis of IMNM
- Autoantibody positive (HMGCR, SRP)
- MRC weakness of ≤ 4/5 in at least 1 proximal muscle group
- CK >1000 IU/L
- Stable doses of corticosteroids, immunosuppressants, or IVIg
- Vaccinated against meningococcus

**Endpoints**
- Primary endpoint: Change from baseline to week 8 in CK
- Secondary endpoints include functional assessments using validated measures, such as:
  - Triple Timed Up and Go (3TUG) Test
  - Proximal Manual Muscle Testing (MMT)
  - Physician and Patient Global Activity Visual Analogue Scales (VAS)
  - Health Assessment Questionnaire (HAQ)
  - Myositis Disease Activity Assessment Tool (MDAAT)
Phase 2 Clinical Trial Site Locations

18 sites selected for participation

United States Locations:
- Bethesda, MD
- Boston, MA
- Orange, CA
- Westwood, KS
- St. Louis, MO
- Jacksonville, FL
- Columbus, OH
- Los Angeles, CA
- Tampa, FL
- Houston, TX
- Philadelphia, PA
- Great Neck, NY
- Memphis, TN

For more information, contact: trials@rapharma.com