Development of a Pipeline of Macrocyclic Peptides for Disorders of the Complement System

6th Annual Peptides Congress
April 24, 2019, London, UK
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 our product candidates, including zilucoplan and PLGA XR formulation of zilucoplan, plans and timing for the presentation of clinical data, expectations surrounding the initiation of a Phase 3 clinical program evaluating zilucoplan for the treatment of gMG and timing thereof, plans and timing for entering into human clinical studies for each of zilucoplan XR and an oral small molecule inhibitor of C5, expectations surrounding the announcement of a new neuromuscular indication for zilucoplan and timing thereof, our market opportunities, the anticipated pricing of our product candidates, if approved, including zilucoplan, and management’s estimates about the potential size and characteristics for the patient populations that our product candidates are targeting. 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 and PLGA XR formulation of zilucoplan, will not successfully be developed or commercialized, 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 April 24, 2019, and Ra Pharma undertakes no duty to update this information unless required by law.
Transforming Complement Therapeutics

- Focused on delivering innovative and accessible therapies to patients with rare diseases
- Macrocyclic / constrained peptides have “come-of-age”
- Zilucoplan: A convenient, self-administered, subcutaneous macrocyclic inhibitor of C5
  - Single, pivotal, 12-week, placebo-controlled, Phase 3 clinical trial in generalized myasthenia gravis (gMG) to initiate in the second half of 2019
- Zilucoplan extended release (XR) program
  - Non-human primate (NHP) studies support once weekly or less frequent dosing
  - Anticipate entering human clinical studies in the first half of 2020
- Exploiting PK/PD advantages of zilucoplan’s improved tissue biodistribution compared to mAbs
  - Small macrocyclic peptides have improved biodistribution to tissues
  - Announcing second tissue-based neuromuscular indication in the second quarter of 2019
- Continue to leverage our proprietary drug discovery engine and expand the pipeline
  - Oral, small molecule inhibitors of complement C5 entering human clinical studies in the first half of 2020
  - Macrocyclic peptide inhibitors of Factor D
  - Merck collaboration: Oral peptide targeting a large CV market opportunity
<table>
<thead>
<tr>
<th></th>
<th>DISCOVERY/ PRE-CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C5 Inhibition Franchise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilucoplan (gMG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilucoplan (PNH)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilucoplan (3rd indication, neurology, TBA 1H19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilucoplan (renal disorders)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilucoplan Extended Release (XR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Small Molecule Inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Factor D Inhibition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orphan Renal Diseases (SC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Complement Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal/Autoimmune/CNS Diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Partnered Program</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Non-Complement Target)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Macrocyclic Peptide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular target with a large market opportunity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Zilucoplan
A Subcutaneously Self-Administered, Macroyclic Peptide Inhibitor of Complement C5

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

**Alternative Pathway**
- Activated by non-self cells
  - C3
  - Factor D, Factor B
- C5a
  - Proinflammatory cytokine

**Classical Pathway**
- Activated by antibody-antigen complexes
  - C1q – C1r – C1s
  - C5
  - C5b
  - C6

**Lectin Pathway**
- Activated by pathogen surfaces
  - C5b6
  - C7, C8, C9
  - Membrane attack complex (MAC)

**Zilucoplan SC**
- Binds C5, blocks cleavage; Blocks MAC assembly

**Eculizumab (IV)**
- Binds C5, blocks cleavage
- Blocks MAC assembly

**Multiple Indications**
- Renal Disorders: Phase 1b positive
- PNH: Phase 2 positive
- gMG: Phase 2 positive
- Neupathies and Myopathies: TBA

**gMG – generalized myasthenia gravis; PNH – paroxysmal nocturnal hemoglobinuria**
Generalized Myasthenia Gravis (gMG) Is a Rare, Debilitating, C5-Mediated Disease¹

**FREQUENCY**
150-250/Million, ~60,000 (US), ~100,000 (EU), ~24,000 (JP)²

**CAUSE**
Autoantibodies block signals from nerves to muscles and complement activation destroys the neuromuscular junction³

**DIAGNOSIS**
Acetylcholine receptor antibody positive²

**CONSEQUENCES**
Serious and progressive
- Significantly impacts quality of life¹,²
- ~80% progress to generalized muscle weakness⁴
- ~20% experience crisis⁵

**TREATMENT**
Sporadic, expensive, and often non-specific
- Cholinesterase inhibitors, corticosteroids, ISTs, thymectomy
- IVIG, PLEX total maintenance costs ~$150,000⁶,⁷ per year
- Eculizumab (Soliris®; Alexion), bi-weekly IV therapy approved in 2017⁸; ~$700,000⁹

**References:**
7. MG Cost Calculator, Data on File.
Extending Complement Inhibition to More Patients with anti-AChR Seropositive Generalized Myasthenia Gravis

Data source: IQVIA market projections (93% retail, 1.5B Rx & Dx claims, CDM ~350 hospitals, PharMetrics health plan 150M pts)
Jan 2016 – Dec 2017 selection period (patients with at least 1 MG diagnosis claim ICD-10 G70.00 or G70.01); 5 years history for treatment and procedures (starting Jan 2013)
Applied best practice eligibility controls and apply appropriate pre-screener/end-treater rules
Used Rx/Dx intersection to project Rx and office-based treatments, and projected hospital utilization of relevant therapies (ie. IVIG, PLEX) using CDM
Segment size projected with Pharmetrics Plus data, therapy usage does not use Pharmetrics Plus; therapy analysis on steroid dosage used to allocate patients on high dose steroid to Uncontrolled

US Prevalence: ~200 per million (~60K pts)

7
**Phase 2 Study Targets Broad gMG Patient Population**

**Broad Patient Population:**
- Generalized MG (Myasthenia Gravis Foundation of America class II-IVa)
- AChR-antibody positive
- Quantitative Myasthenia Gravis (QMG) score of ≥ 12
- Stable doses of corticosteroids and/or immunosuppressants
- No requirement to be “refractory” or have failed multiple prior therapies

**Endpoints:**
- Primary: Change in QMG score from baseline to week 12
- Key Secondary: Change in MG-ADL score from baseline to week 12
- Pre-specified significance testing at 1-sided alpha of 0.1

**Enrollment:** 44 patients (vs. target of 36)

---

Randomized, double-blind, placebo-controlled, multi-center study followed by an open-label, long-term extension (LTE)
Baseline Characteristics Confirm Breadth of gMG Study Population

<table>
<thead>
<tr>
<th>Variable</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>
</thead>
<tbody>
<tr>
<td>Age, mean years (± SD)</td>
<td>48 (15.7)</td>
<td>46 (15.7)</td>
<td>55 (15.5)</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>4 (27%)</td>
<td>7 (47%)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Race, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• White</td>
<td>12 (80%)</td>
<td>13 (87%)</td>
<td>11 (79%)</td>
</tr>
<tr>
<td>• Asian</td>
<td>1 (7%)</td>
<td>0</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>• Black or African American</td>
<td>2 (13%)</td>
<td>2 (13%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>MGFA Class at Screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• II</td>
<td>7 (47%)</td>
<td>8 (53%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>• III</td>
<td>8 (53%)</td>
<td>10 (67%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>• IVa</td>
<td>0</td>
<td>0</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Duration of Disease, mean years (min, max)</td>
<td>8.0 (0.1, 20.9)</td>
<td>8.7 (1.6, 24.1)</td>
<td>8.3 (0.5, 26.0)</td>
</tr>
<tr>
<td>Baseline QMG Score, mean (± SD)</td>
<td>18.7 (4.0)</td>
<td>18.7 (4.0)</td>
<td>19.1 (5.1)</td>
</tr>
<tr>
<td>Baseline MG-ADL Score, mean (± SD)</td>
<td>8.8 (3.6)</td>
<td>6.9 (3.3)</td>
<td>7.6 (2.6)</td>
</tr>
<tr>
<td>Baseline MG Composite Score, mean (± SD)</td>
<td>18.7 (5.7)</td>
<td>14.5 (6.3)</td>
<td>14.6 (6.3)</td>
</tr>
<tr>
<td>Baseline MGOq15r Score, mean (± SD)</td>
<td>15.9 (7.4)</td>
<td>19.1 (5.0)</td>
<td>16.5 (7.3)</td>
</tr>
<tr>
<td>Prior MG Therapies (Standard of Care)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pyridostigmine, n(%)</td>
<td>14 (93%)</td>
<td>15 (100%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>• Corticosteroids, n(%)</td>
<td>13 (87%)</td>
<td>13 (87%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>• Immunosuppressants, n(%)</td>
<td>12 (80%)</td>
<td>12 (80%)</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>Prior IVIG, n(%)</td>
<td>9 (60%)</td>
<td>8 (53%)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Prior Plasma Exchange, n(%)</td>
<td>7 (47%)</td>
<td>9 (60%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Prior Thymectomy, n(%)</td>
<td>5 (33%)</td>
<td>8 (53%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Prior MG Crisis Requiring Intubation, n(%)</td>
<td>3 (20%)</td>
<td>4 (27%)</td>
<td>2 (14%)</td>
</tr>
</tbody>
</table>

High Unmet Medical Need

Non-Refractory Patients Included

- 9% no prior steroids
- 25% no prior ISTs
- 39% no prior IVIG
- 48% no prior PLEX
Primary and Key Secondary Endpoints Met with 0.3 mg/kg Zilucoplan Dose: Rapid, Clinically Meaningful, and Statistically Significant Reductions in QMG and MG-ADL

Pre-specified significance testing at 1-sided alpha of 0.1 with LOCF ANCOVA p values shown; error bars denote standard errors of least squares mean; mITT
Patients Can Achieve Minimal Symptom Expression by Week 12

Minimal symptom expression (MSE) = Achieving MG-ADL score of 0 or 1

23% of patients (placebo-corrected) achieved MSE in 12 weeks in 0.3 mg/kg zilucoplan arm

## Safety and Tolerability Profile Supports 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>
</thead>
<tbody>
<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>2</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>3</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
Zilucoplan in gMG: Phase 2 Top-Line Data Summary

- Positive Phase 2 study in broad gMG population (not restricted to “refractory”)
- Primary and key secondary endpoints met with clinically meaningful and statistically significant reductions in QMG and MG-ADL in both 0.3 mg/kg and 0.1 mg/kg dose groups
- Magnitude and speed of effect, no rescue therapy required, and higher rate of minimal symptom expression all favor 0.3 mg/kg dose over 0.1 mg/kg dose for Phase 3
- Favorable safety and tolerability profile with no early withdrawals in the study; Safety and PK/PD profile consistent with Phase 1 healthy volunteer and Phase 2 PNH studies
- Single, pivotal, 12-week, placebo-controlled, Phase 3 clinical trial to initiate in 2H19
- Phase 2 data, including long-term extension data, to be presented at the 2019 American Academy of Neurology Annual Meeting, Philadelphia, PA, from May 4 to 10, 2019
Development of Zilucoplan XR
Poly(D,L-lactic-co-glycolic Acid) (PLGA): A Validated Delivery Platform for Peptides

- Poly(D,L-lactic-co-glycolic acid) (PLGA)/poly (lactic acid) (PLA) microspheres/nanoparticles are one of the most successful drug delivery systems for extended release

- An established platform for sustained release of parenteral peptides in both adults and pediatric patients with at least 15 products available on the US market, e.g.:
  - Bydureon® (exenatide)
  - Lupron / Lupron Depot® (leuprolide)
  - Lupron depot PED® (leuprolide)
  - Sandostatin® LAR (octreotide)
  - Trelstar® (triptorelin)
  - Risperdal Consta® (risperidone)
  - Signifor® LAR (parsireotide)
  - Zoladex® (goserelin)

- PLGA XR formulation of zilucoplan is consistent with Ra’s life-cycle extension vision to improve accessibility and simplify disease management
  - Delivers stable concentrations of drug with once weekly or less frequent dosing
  - Single, low volume injection without requirement for on body infusion devices
  - Therapeutic concentrations of drug maintained at all times without significant fluctuation in PD
  - Potential for room temperature storage
  - Low cost-of-goods to support improved accessibility
PLGA XR Formulation of Zilucoplan
Designed to Have Uniform Microsphere Morphology with High Drug Loading and Homogeneous Distribution

Zilucoplan PLGA microsphere (A) Surface morphology by scanning electron microscopy and (B) Drug distribution by Na+ Energy Dispersive X-Ray Spectroscopy*

Optimization of process has delivered a uniform particle with homogenous distribution of zilucoplan throughout microspheres

- Target drug load achieved: Morphology and size range enable good syringeability
- Homogeneous distribution of drug in particle expected to ensure predictable drug release with minimal burst (<5%)

*Data on record at Ra Pharma
NHP and Human PK/PD
Highly Comparable Across Species

Comparable concentration dependence of complement inhibition observed in pre-clinical NHP and Phase 1 and Phase 2 human clinical studies

For reference across species, vertical dotted line represents clinical trough concentration for daily 0.3 mg/kg

*Data on record at Ra Pharma
Comparison of PLGA XR formulation of zilucoplan Q1W PD to zilucoplan IR daily in NHP and myasthenia gravis patients

- Zilucoplan IR dose (Phase 2 MG): 0.3 mg/kg
- Zilucoplan IR dose (NHP): 0.3 mg/kg
- Zilucoplan XR dose (NHP): Dose A and 0.3x Dose A

Graph showing % Hemolysis over Time (Day) with different doses and formulations.
Dose-to-Man Modeling at Steady State
Release Profile of PLGA XR Formulation of Zilucoplan Q1W Indicates Potential to Deliver Meaningful Dose Efficiency

Human Dose Projection
• Human target mediated drug disposition pharmacokinetic model
• Input profile based upon deconvolution of zilucoplan XR release in non-human primates
• Green dashed lines: Zilucoplan IR concentration range at steady state in Phase 2 gMG study

Model indicates XR dose of 100 mg (Q1W) has potential to maintain meaningful drug concentrations
Approximately 33% dose efficiency realized compared to 7 daily doses of immediate release product*

*Based on 70 kg adult and 0.3 mg/kg per day for current daily product
The Zilucoplan Life Cycle – Positioned for Success

Large mAb (140 kDa)
Last Line
Long Infusion (~1 hr)
High Volume IV (>90mL)
Exclusive

Rising Expectations for Complement Inhibition

Small Peptide (3 kDa)
Earlier Use
Brief Injection (5-8 sec.)
Convenient SC (~0.5 mL)
Accessible

Today

Zilucoplan IR

Zilucoplan XR

Once weekly or less frequent dosing
Simple SC injection
Low volume
No on-body infusion device
Advantages of a Peptide-Based Approach to MG and Other Tissue-Based Diseases
## Rodent QWBA: Size and Biodistribution to Muscle
Zilucoplan Has Improved Biodistribution into Tissue vs. Typical mAb

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Antibody Biodistribution¹ (%)</th>
<th>Zilucoplan Biodistribution² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>14.9</td>
<td>37.5</td>
</tr>
<tr>
<td>Heart</td>
<td>10.2</td>
<td>22.9</td>
</tr>
<tr>
<td>Muscle</td>
<td>3.97</td>
<td>7.0</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>5.22</td>
<td>10.9</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>5.03</td>
<td>21.7</td>
</tr>
<tr>
<td>Spleen</td>
<td>12.8</td>
<td>15.5</td>
</tr>
<tr>
<td>Liver</td>
<td>12.1</td>
<td>27.1</td>
</tr>
<tr>
<td>Bone</td>
<td>7.27</td>
<td>15.3</td>
</tr>
<tr>
<td>Stomach</td>
<td>4.98</td>
<td>8.5</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>8.46</td>
<td>12.8</td>
</tr>
<tr>
<td>Fat</td>
<td>4.78</td>
<td>16.2</td>
</tr>
<tr>
<td>Brain</td>
<td>0.35</td>
<td>0.9</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6.4</td>
<td>15.8</td>
</tr>
<tr>
<td>Testes</td>
<td>5.88</td>
<td>15.5</td>
</tr>
<tr>
<td>Thymus</td>
<td>6.62</td>
<td>7.8</td>
</tr>
</tbody>
</table>

1. Shah DK, Betts AM. Antibody biodistribution coefficients: Inferring tissue concentrations of monoclonal antibodies based on the plasma concentrations in several preclinical species and human. mAbs 2013; 5:297-305
2. Ra Internal Data – Rat QWBA Study using radiolabeled zilucoplan; Data represent tissue AUC0-24 as a percentage of Plasma
Modeling Permeability Across the Basal Lamina
Zilucoplan Exhibited Improved Diffusion in Matrigel Model

**Schematic of neuromuscular junction**

**Model of basal lamina diffusion using matrigel membrane**

**Zilucoplan demonstrates a 4x improvement in permeability across matrigel membrane at 24 hours compared with eculizumab**


**Data on record at Ra Pharma**
Transforming Complement Therapeutics

- Focused on delivering innovative and accessible therapies to patients with rare diseases
- Macrocyclic / constrained peptides have “come-of-age”
- Zilucoplan: A convenient, self-administered, subcutaneous macrocyclic inhibitor of C5
  - Single, pivotal, 12-week, placebo-controlled, Phase 3 clinical trial in generalized myasthenia gravis (gMG) to initiate in the second half of 2019
- Zilucoplan extended release (XR) program
  - Non-human primate (NHP) studies support once weekly or less frequent dosing
  - Anticipate entering human clinical studies in the first half of 2020
- Exploiting PK/PD advantages of zilucoplan’s improved tissue biodistribution compared to mAbs
  - Small macrocyclic peptides have improved biodistribution to tissues
  - Announcing second tissue-based neuromuscular indication in the second quarter of 2019
- Continue to leverage our proprietary drug discovery engine and expand the pipeline
  - Oral, small molecule inhibitors of complement C5 entering human clinical studies in the first half of 2020
  - Macrocyclic peptide inhibitors of Factor D
  - Merck collaboration: Oral peptide targeting a large CV market opportunity