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 our 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, 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 and statements regarding the completion and anticipated proceeds of the proposed offering and the use of the net proceeds of the proposed offering. 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 our 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 October 2, 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, complement-mediated diseases
- Zilucoplan: A convenient, self-administered, subcutaneous complement C5 inhibitor
  - Generalized myasthenia gravis (gMG): Successful Phase 2 study in a broad spectrum of patients with gMG; Phase 3 clinical trial ongoing
  - Immune-mediated necrotizing myopathy (IMNM): Phase 2 clinical trial ongoing
  - Amyotrophic lateral sclerosis (ALS): Selected for HEALEY ALS Platform Trial by Sean M. Healey & AMG Center for ALS at Mass General
  - Positive Phase 1b trials: Ethno-bridging (Japan) and in patients with renal impairment; Support further development with no need for dose modification
- Advancing a portfolio of investigational C5 inhibitors in pre-clinical development
  - XR: PLGA and FluidCrystal® (FC) XR formulations of zilucoplan achieved rapid and sustained pharmacodynamic inhibition of complement C5 in non-human primates, supporting once weekly or less frequent dosing in clinical trials
  - SMi: First-in-class oral small molecule C5 inhibitor
- Proprietary drug discovery engine
  - Trillion member, highly diverse, synthetic macrocyclic peptide libraries; Diversity and specificity of mAbs with the pharmacologic advantages of small molecules
- Merck Collaboration: Oral peptide targeting a large CV market opportunity
### Pipeline Programs

#### C5 Inhibition

<table>
<thead>
<tr>
<th>Program</th>
<th>DISCOVERY/PRE-CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zilucoplan (gMG)</td>
<td></td>
<td>Phase 3 RAISE trial ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilucoplan (IMNM)</td>
<td></td>
<td>Phase 2 trial ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilucoplan (ALS)</td>
<td></td>
<td>Phase 2/3 HEALEY ALS Platform Trial planned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilucoplan (renal disorders)</td>
<td></td>
<td>Phase 1b trial complete</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>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Factor D Inhibition

- Orphan Renal Diseases (SC)

#### Other Complement Inhibitors

- Renal/Autoimmune/CNS Diseases

#### Partnered Program

- (Non-Complement Target)
  - Oral Macroyclic Peptide
    - Cardiovascular target with a large market opportunity
    - Phase 1 trial ongoing
Zilucoplan: A Self-Administered, Subcutaneous, Macroyclic 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
  - C1q – C1r – C1s

**Lectin Pathway**
- Activated by pathogen surfaces
  - C5
  - C5b
  - C6
  - C7, C8, C9
  - Membrane attack complex (MAC)

**Eculizumab (IV)**
- Binds C5, blocks cleavage
- Proinflammatory cytokine
- Zilucoplan (SC)
  - Binds C5, blocks cleavage; Blocks MAC assembly
  - Half-life extender
  - 15 amino-acid cyclic peptide inhibitor of C5

**Multiple Indications**
- **gMG**: Phase 2 positive ✓
  - Phase 3 ongoing
- **IMNM**: Phase 2 ongoing
- **ALS**: Platform trial planned
- **PNH**: Phase 2 positive ✓
- **Renal Disorders**: Phase 1b positive ✓

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**Abbreviations**
- gMG – generalized myasthenia gravis
- IMNM – immune-mediated necrotizing myopathy
- ALS – amyotrophic lateral sclerosis
- PNH – paroxysmal nocturnal hemoglobinuria

---

**Notes**
- Multiple validated indications, pipeline-in-a-product potential
- Zilucoplan: A Self-Administered, Subcutaneous, Macroyclic Peptide Inhibitor of Complement C5
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
Generalized Myasthenia Gravis (gMG) Is a Rare, Debilitating, C5-Mediated Disease

References:
7. MG Cost Calculator, Data on File.
8. Eculizumab (Soliris®; Alexion), bi-weekly IV therapy approved in 2017; ~$700,000 per year.
Significant Disease Burden for Most Patients with gMG Despite Ongoing Treatment

- **Activities of Daily Living (ADL)** - talking, chewing, swallowing, breathing, brush teeth, comb hair, arise from chair, double vision, eyelid droop

- ~70% of patients with ADL >6 feel their treatment goals are not being met

Patients Dissatisfied with Current Treatments

- Prednisone adverse effects extremely common & intolerable (more than 90% of patients reported adverse events)

- Treatment dissatisfaction: 1) too much time to start working; 2) does not relieve symptoms; 3) inconvenient

- ~40% of patients do not feel in control of their condition, treatments do not target underlying disease

---

3. MGFA. MG Activities of Daily Living (MG-ADL) profile.
Treatment Paradigm: Target Complement-Mediated Damage Earlier

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 for pathway analyses (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)

Acetylcholinesterase Inhibitor → Steroids → Immunosuppressive Therapies → IVIG/PLEX

>70% of these patients
>20mg/day steroids AND at least 1 IST

>90% of these patients
chronic IVIG, PLEX

Uncontrolled
>20K pts ~ 35%

Last Line
<10K pts ~ 15%

Zilucoplan Target Population

Opportunity to Treat
~30K Patients (U.S. Only) with AChR+ gMG

MG Diagnosis

Opportunities

Acetylcholinesterase Inhibitor
Steroids
Immunosuppressive Therapies
IVIG/PLEX

REGAIN Population
(Eculizumab)
Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of Zilucoplan in a Broad Generalized Myasthenia Gravis Population

**Broad Patient Population:**
- Generalized myasthenia gravis (MGFA class II-IVa)
- Acetylcholine receptor (AChR) antibody positive
- QMG score of ≥12
- Stable doses of corticosteroids and/or immunosuppressants
- No requirement to be “refractory” or to have failed multiple prior therapies
- Patients must be vaccinated against meningococcus

**Endpoints:**
- **Primary:** Change in QMG score from baseline to week 12
- **Secondary:** Change in MG-ADL, MG Composite, and MGQoL15r scores from baseline to week 12
- Pre-specified significance testing at a 1-sided alpha of 0.1

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

**Diagram:**
- 0.3 mg/kg SC + SOC (n=14)
- 0.1 mg/kg SC + SOC (n=15)
- Placebo + SOC (n=15)
- Placebo arm randomized 1:1 to receive 0.3 mg/kg (n=7) or 0.1 mg/kg (n=7)
- Open-Label Extension (n=42)

QMG, Quantitative Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MGQoL15r, 15-item Myasthenia Gravis Quality-of-Life revised scale; SC, subcutaneous; SOC, standard of care.
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>MGFAT Class at Screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>7 (47%)</td>
<td>5 (33%)</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 MGQoL15r 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
Pharmacokinetic and Pharmacodynamic Results
Support Evaluation 0.3 mg/kg Dose of Zilucoplan
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).

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; MGQoL15r, 15-item Myasthenia Gravis Quality-of-Life revised scale; SEM, standard error of the mean.
Pre-Specified Pooled Analysis of MG-ADL at Week 12 Satisfied 2-Sided p<0.05

In Phase 2, zilucoplan met Phase 3 primary endpoint (MG-ADL at 12 weeks) with similar magnitude and statistical significance as eculizumab in Phase 3 REGAIN study at 26 weeks*

LOCF ANCOVA 2-sided p value shown; error bars denote standard errors of least squares mean; mITT
* Placebo-corrected change in MG-ADL at 26 weeks in REGAIN study: -1.9 LOCF ANCOVA p=0.039; ref. Howard et al AANEM 2016; For Informational Purposes: Differences exist between trial designs and subject populations. Ra Pharma has not conducted any head-to-head trials comparing zilucoplan to eculizumab.
Minimal Symptom Expression Observed 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

# 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>
</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>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
Zilucoplan: A Convenient Complement Inhibitor for a Broad gMG Population

Administration | Tx Time | Population | Mechanism | QMG, ADL
---|---|---|---|---
Zilucoplan | ~0.5 mL (3 kDa) SC daily self-admin | 5-8 sec. | Uncontrolled MG (~30k) C5 Cyclic Peptide | QMG | @ 12wks: -2.8 @ 24wks: -1.7
| | | | | ADL | @ 12wks: -2.3 @ 24wks: -1.9

Eculizumab | 120 mL (140 kDa) Intravenous infusion every 14 days | 45 min. | Refractory MG (~3-5k) C5 mAb | QMG | @ 12wks: ~-2.5 @ 26wks: ~-3.0
| | | | | ADL | @ 12wks: ~-1.7 @ 26wks: ~-1.9

1Soliris QMG, ADL at 12wk estimated (Ref. Howard et al. Lancet 2017)
2Soliris QMG, ADL improvement at 26wks (Ref. Howard et al. Lancet 2017)
3Soliris Highlights of Prescribing Information; http://alexion.com/Documents/Soliris_USPI.aspx; For Informational Purposes: Differences exist between trial designs and subject populations. Ra Pharma has not conducted any head-to-head trials comparing zilucoplan to eculizumab.
Pivotal, 12-Week, Placebo-Controlled Phase 3 Clinical Trial in Generalized Myasthenia Gravis

**Inclusion Criteria:**
- Generalized myasthenia gravis (MGFA class II to IV)
- Acetylcholine receptor antibody positive
- MG ADL score ≥ 6 and QMG total score ≥ 12
- Stable doses of corticosteroids and/or immunosuppressants
- No requirement to be “refractory” or to have failed multiple prior therapies
- Patients must be vaccinated against meningococcus

**Primary Endpoint:**
- Change from baseline to week 12 in MG-ADL total score, *p<0.05

**Enrollment:** ~130 patients

---

**Diagram:**
- **Screening**
- **1:1 Randomization** n = 130
- **Main Study Period (12 Weeks)**
  - Placebo + Standard of Care
  - 0.3 mg/kg SC + Standard of Care
- **Open-Label Long-Term Extension (Active Drug)**

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Ra Pharma
Improved Biodistribution of Zilucoplan 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

Rodent quantitative whole-body autoradiography (QWBA) studies
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
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/Million
US: ~6,300 cases
EU: ~6,500 cases
Japan: ~2,500 cases

Epidemiology:
Age of onset, typically 40 to 60 years, predominantly affects females

Idiopathic Inflammatory Myopathies
- Anti-synthetase syndrome
- Dermatomyositis
- Inclusion body myositis

Anti-SRP
- ~70%

Anti-HMGCR
- ~30%

Ab negative

**IMNM: A Severe and Debilitating Disease of Muscle Necrosis**

**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

**Key Features**

- 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

**Subtypes**

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

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

**References**

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

Healthy Muscle Tissue

Anti-SRP or Anti-HMGCR–Mediated Complement Activation

Muscle Cell

Complement Cascade

Anti-SRP or Anti-HMGCR binding

C5

C5a

C5b

Formation of MAC on cells

Necrotic Muscle Tissue

Creatine kinase release

Creatine kinase release

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 IMNM\(^1\)

Muscle fibers | Muscle fibers | Capillaries | Vascular endothelial and smooth muscle layers of the small artery wall | Small vein wall
---|---|---|---|---

[Images of muscle fibers, capillaries, vascular endothelium, and small vein wall]

Phenotypic rescue of IMNM-induced muscle weakness in complement-deficient mice\(^2\)

Muscle weakness in mice can be induced with sera from patients with IMNM\(^2\)

Pathogenicity of patient serum is dependent on the presence of complement\(^2\)

Current Treatment Paradigm for IMNM Is Non-Specific and Inadequate

There are currently **no approved treatments** for IMNM\(^1\)

Despite intense immunosuppression, ~52 - 66% of patients show progression and incomplete recovery at two years\(^2\)

Multiple specialties are involved in IMNM management

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**1ST LINE**

**Anti-SRP Myopathy**

- Corticosteroids
  - Prednisone/prednisolone (oral)
  - or Methylprednisolone (IV)\(^a\)

**Anti-HMGCR Myopathy**

- Immunosuppressives
  - Methotrexate
  - Azathioprine
  - Mycophenolate mofetil\(^b\)

- Rituximab (IV)\(^c\)

- IVIG\(^c\)

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\(^a\)Used in severe cases of IMNM.

\(^b\)Azathioprine/mycophenolate mofetil may be used in the case of methotrexate intolerance.

\(^c\)In patients with anti-SRP myopathy, methotrexate and rituximab are generally considered before IVIG. In patients with anti-HMGCR myopathy, methotrexate and IVIG are generally considered before rituximab; IVIG may be used as maintenance treatment on a case-by-case basis.

Phase 2 Clinical Trial Is Designed to 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)

**Diagram**
- **Screening**
- **1:1 Randomization**
  - Placebo + Standard of Care (n=12)
  - 0.3 mg/kg SC + Standard of Care (n=12)
- **Long-Term Extension (Active Drug)**
- **Long-Term Extension**

Main Study Period (8 Weeks)

Sources: Ra Pharma
Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disease. ALS is a severe neurodegenerative disorder characterized by the loss of upper and lower motor neurons, resulting in progressive muscle weakness, atrophy, and eventually partial or total paralysis.

Presentation and Prognosis

Onset of ALS
- Spinal: 67%
- Bulbar: 33%
  - eg, limbs affected

Causes of ALS
- Sporadic: 90%–95%
- Familial: 5%–10%

Pathophysiology
- Neurodegeneration: involvement of upper (cortico-spinal) and lower (bulbospinal) motor neurons
- Gliosis: reactive inflammation of astrocyte and microglial cells

Symptoms
- Focal symptom onset:
  - Upper or lower limb fatigable or persistent muscle weakness
- Muscle atrophy, stiffness
- Dysarthria, dysphagia
- Fasciculations, cramps, spasticity
- Respiratory failure
- Progressive symptoms:
  - Global muscle weakness
  - Paralysis
- Death by respiratory failure

2–5 years average life expectancy
80% mortality within 5 years

ALS Is a Rare Disease With Few Therapeutic Options

**PREVALENCE**
- 50-70 per 1 million people
- United States: ~20,000
- Europe*: ~22,000
- Japan: ~8,000

**INCIDENCE**
- ~20 per 1 million people
- United States: ~6,000
- Europe*: ~6,500
- Japan: ~2,400

Mean age at diagnosis: 55–65 yr

There is **no cure** for ALS:
- Riluzole
- Edaravone

Only **2** FDA-approved drugs:

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*Represented by Spain, France, Italy, Germany, and United Kingdom.

Complement MAC Proteins Are Associated With Neuroinflammation in Patients With ALS

Activation of the immune system, including a high expression of complement proteins, has been observed in the spinal cord and motor neurons of patients with ALS\(^1,2\)

\(\text{P value calculated using a nonparametric Wilcoxon rank-sum test. sC5b-9, serum complement components C5b through C9, also known as membrane attack complex (MAC).}\)

PLGA XR Formulation of Zilucoplan Designed to Have Uniform Microsphere Morphology with High Drug Loading and Homogeneous Distribution

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 designed to enable predictable drug release with minimal burst (<5%)

*Data on record at Ra Pharma*
Zilucoplan PK/PD Have Been Highly Comparable Across Non-Human Primate Pre-Clinical and Human Clinical Studies

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
Once-Weekly Administration of PLGA XR Formulation of Zilucoplan Rapidly Achieved Target C5 Inhibition Equivalent to Daily Administration

**Comparison of PLGA XR formulation of zilucoplan Q1W PD to zilucoplan IR daily in NHP and myasthenia gravis patients**

![Graph showing comparison of PLGA XR formulation of zilucoplan to daily administration in NHP and myasthenia gravis patients.]

**Inhibition of complement activity following a single subcutaneous dose of PLGA XR formulation of zilucoplan in cynomolgus monkeys as measured by an ex-vivo sheep red blood cell assay.**
FC XR Formulation of Zilucoplan Rapidly Achieved and Maintained Target Levels of Complement Inhibition for at Least Seven Days in NHPs

- Exclusive worldwide license agreement with Camurus AB for proprietary FluidCrystal® (FC) technology

- FC injection depot is a lipid-based liquid that absorbs interstitial aqueous body fluid and transforms to gel-like phases in situ, encapsulating the active substance

- FC technology designed to enable disease control with a simple presentation:
  - Low volume, SC self-administration
  - Room-temperature stable
  - No need for IV loading

- FC XR formulation of zilucoplan achieved rapid and sustained pharmacodynamic inhibition of complement C5 in non-human primates, supporting the potential for at least once weekly dosing

Inhibition of complement activity following a single subcutaneous dose of FC XR formulation of zilucoplan in cynomolgus monkeys as measured by an ex-vivo sheep red blood cell assay (Mean±SEM, n=4).
Small molecule C5 inhibitors (SMi) do not bind to mouse complement C5
- Immunodeficient mice transplanted with human hepatocytes provide circulating human complement

- Oral dosing of SMi resulted in full blockade of *ex vivo* zymosan-mediated C5 activation (incubation in whole blood)
Array of C5 Inhibitor Assets Provides an Opportunity to Build a Transformative Pipeline in Neurology

Neurology Disease Targets, Systemic & Local C5

- Neuromuscular
- Neuropathies/Myopathies
- Neurodegenerative

C5 Inhibitor Lifecycle

- Zilucoplan QD: Once daily SC small peptide inhibitor, designed to inhibit C5 systemically and locally
- Zilucoplan XR: Added convenience of SC once weekly
- Oral Small Molecule C5 Inhibitor: Highly potent, orally available

Potential of a Peptide Inhibitor in Tissue-Based C5 Diseases and a First-in-Class Oral Small Molecule
Focused on delivering innovative and accessible therapies to patients with rare, complement-mediated diseases

Zilucoplan: A convenient, self-administered, subcutaneous complement C5 inhibitor

- **Generalized myasthenia gravis (gMG):** Successful Phase 2 study in a broad spectrum of patients with gMG; Phase 3 clinical trial ongoing
- **Immune-mediated necrotizing myopathy (IMNM):** Phase 2 clinical trial ongoing
- **Amyotrophic lateral sclerosis (ALS):** Selected for HEALEY ALS Platform Trial by Sean M. Healey & AMG Center for ALS at Mass General
- **Positive Phase 1b trials:** Ethno-bridging (Japan) and in patients with renal impairment; Support further development with no need for dose modification

Advancing a portfolio of investigational C5 inhibitors in pre-clinical development

- **XR:** PLGA and FluidCrystal® (FC) XR formulations of zilucoplan achieved rapid and sustained pharmacodynamic inhibition of complement C5 in non-human primates, supporting once weekly or less frequent dosing in clinical trials
- **SMi:** First-in-class oral small molecule C5 inhibitor

Proprietary drug discovery engine

- Trillion member, highly diverse, synthetic macrocyclic peptide libraries; Diversity and specificity of mAbs with the pharmacologic advantages of small molecules

Merck Collaboration: Oral peptide targeting a large CV market opportunity