Transforming Complement Therapeutics

October 2018
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 (RA101495 SC), the anticipated timing of topline data read-outs for our Phase 2 clinical trials of zilucoplan, beliefs regarding clinical trial data, statements regarding trial design, timeline and enrollment of our ongoing and planned clinical programs, including without limitation our Phase 3 trial of zilucoplan for the treatment of PNH, upcoming milestones, including without limitation the release of top-line data in gMG around year-end 2018, and expectations surrounding USAN approval of the name zilucoplan, our market opportunities, 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, will not successfully be developed or commercialized; the risk that topline results as of February 7, 2018 from the Company’s global Phase 2 clinical program evaluating zilucoplan for the treatment of PNH may not be indicative of final study results; the risk that USAN does not approve the name zilucoplan; 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. All information in this presentation is as of October 2, 2018, and Ra Pharma undertakes no duty to update this information unless required by law.
Focused on rare hematologic, neurologic, and renal indications

Zilucoplan (RA101495 SC): Convenient, self-administered, subcutaneous C5 inhibitor
- Phase 3 studies in paroxysmal nocturnal hemoglobinuria (PNH) planned
- Phase 2 study in generalized myasthenia gravis (gMG):
  - Enrollment completed (ahead of schedule, Aug. 2018), target surpassed (n=44 pts vs. 36 pts)
  - Top line data read-out around year-end 2018
- Positive Phase 1b PK study in renally impaired patients; no dose adjustment required

Portfolio of C5 inhibitors in pre-clinical development
- Extended release formulation of zilucoplan
- First-in-class oral small molecule C5 inhibitor

Powerful proprietary drug discovery engine
- Trillion member, highly diverse, synthetic macrocyclic peptide libraries
- Diversity and specificity of mAbs with the pharmacologic advantages of small molecules

Collaboration with Merck for an oral peptide targeting a large CV market opportunity
Opportunities in Complement Inhibition

**Alternative Pathway**
- Activated by non-self cells
  - C3
  - Factor D
  - Factor B (non-self cells)

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

**Lectin Pathway**
- Activated by pathogen surfaces
  - C5
  - C5b

**Multiple Indications**
- **PNH**: Rupture of RBC
- **gMG**: Destruction of neuromuscular junction
- **aHUS**: Hemolytic anemia, thrombocytopenia, and renal failure
- **LN**: Inflammation of kidney glomerulus

**Signaling Pathways**
- **C5a**: Proinflammatory cytokine
- **Eculizumab**: Binds C5
- **Zilucoplan**: Binds C5 & C5b (Membrane attack complex [MAC])
# Pipeline Programs

<table>
<thead>
<tr>
<th>C5 Inhibition Franchise</th>
<th>DISCOVERY/ PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>zilucoplan (PNH)</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 (renal; aHUS/LN)</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>Factor D Inhibition</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>Other Complement Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular/Autoimmune/CNS diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partnered Program</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Non-Complement target)</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>
</tbody>
</table>
| (Cardiovascular target with a large market opportunity) | | | | |.

<table>
<thead>
<tr>
<th>Partnered Program (Non-Complement target)</th>
<th>DISCOVERY/ PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
</tr>
</thead>
</table>
| Oral Macrocyclic Peptide (Cardiovascular target with a large market opportunity) | | | | |.
Zilucoplan – Positioned for Success

Large mAb (140 kDa) → Rising Expectations for Complement Inhibition → Small Peptide (3 kDa)

Last Line → Earlier use → Brief Injection (5-8 sec.)

Long Infusion (~1 hr) → Convenient SC (~0.5 mL)

High Volume IV (90-120 mL) → Accessible

Exclusive → Today → Zilucoplan

Today

Zilucoplan

Rising Expectations for Complement Inhibition
Zilucoplan – Building a Pipeline within a Product

Expanded Market Opportunities Through Convenient Complement Control

**Potential Future Indications**
- ANCA Vasculitis
- Lupus Nephritis
- HELLP
- NMO
- TMA
- aHUS
- gMG
- PNH

**Development**
- **Ph1b**
- **Ph2**

**Potential 1st line option to**
- urgently treat acute or progressive TMA
- target complement-mediated damage earlier
- treat all naïve and most switch patients
Paroxysmal Nocturnal Hemoglobinuria (PNH) – Rare, Life-threatening, C5-Mediated Disease

**Frequency**
- **~ 8,000 to 10,000 people in North America and Europe**
- **~1,000 to 2,000 in Japan**

**Cause**
- Spontaneous mutations in the PIG-A gene in red blood cells (RBCs) cause PNH

**Natural History**
- Early diagnosis and intervention is critical
  - Variability of PNH delays diagnosis, often up to 10 years
  - 35% of PNH patients die within 5 years of diagnosis
  - Median survival after diagnosis is 10 years

**Treatment**
- Expensive and exclusive
  - Anti-complement C5 monoclonal antibody [eculizumab (Soliris®); Alexion]
  - Biweekly IV infusion; Approximate annual cost $600,000

**Consequences**
- Serious and progressive
  - Life-threatening complications in PNH include thromboses, renal insufficiency, and other organ damage

---

Estimated 1.3 per million per year newly diagnosed patients

---

**Complement-mediated hemolysis underlies progressive morbidities and mortality in PNH**

- PIG-A mutation results in surface complement deposition and activation due to loss of complement regulators (CD59, CD55)
- C3b, a fragment of complement C3, is deposited on RBC surface
- Convertases containing C3b activate C5 leading to MAC formation

![Diagram of complement-mediated hemolysis](image-url)
Zilucoplan PNH Program - Phase 2 Study Design

**Loading dose:** 0.3mg/kg SC on Day 1

**Starting dose:** 0.1mg/kg SC once daily for the first 2 weeks

**Up-titration:** from the week 2 visit onwards, if LDH was ≥ 1.5xULN, the dose was increased to 0.3mg/kg SC once daily
Zilucoplan Phase 2 Study in Treatment Naïve PNH Patients – Rapid, Robust, Sustained Reduction of LDH

**Dose Dependence of Complement Inhibition**

- **Zilucoplan Plasma concentration (ng/mL)**
- **% Hemolysis**

**Comparable LDH Reduction to Eculizumab**

- ****Relative overdosing of eculizumab during weekly loading period coincides with relative underdosing of zilucoplan during dose-titration.

*Not a head-to-head comparison.

**Weekly eculizumab loading period**

**Comparable LDH Reduction to Eculizumab**

- **Phase 2 PNH; 0.1 mg/kg**
- **Phase 2 PNH; 0.3 mg/kg**

**Relative overdosing of eculizumab during weekly loading period coincides with relative underdosing of zilucoplan during dose-titration.**

**Phase 1 HV**

**Phase 2 PNH; 0.1 mg/kg**

**Phase 2 PNH; 0.3 mg/kg**

**% Hemolysis**

**Zilucoplan Plasma concentration (ng/mL)**

**LDH (U/L)**

**Weeks**

**Zilucoplan N = 10 10 10 10 10 10 10 10 9 9 7**

*Not a head-to-head comparison.

**Weekly eculizumab loading period**
Zilucoplan Phase 2 Study in Eculizumab Switch
Success in Clearly Defined Sub-Population

Robust LDH Control in Transfusion-Independent Patients

Reticulocyte Count at Time of Switching is an Important Predictor of Switch Success

- Transfusion Dependent
- Transfusion Independent

LDH (U/L)

Week

Baseline 1 2 3 4 6 8 10 12 16 20 24

n= 11 10 9 7 6 4 2 1 1 7 early withdrawals

n= 5 5 5 4 4 4 2 2 2 1 early withdrawal

1.5x ULN

2xULN

ULN
Zilucoplan Phase 2 PNH Program – Safety and Tolerability

- Long-term RA101495 SC exposure: > 60 weeks of dosing
- No dosing interruptions, down-titrations, or discontinuations due to tolerability
- No meningococcal infections observed
- No thromboembolic events observed
- ~100% compliance with once daily subcutaneous self-administration at home observed (monitored remotely by smartphone)
- Majority of adverse events observed deemed unrelated to study drug
- Most common related adverse event observed has been headache
- Well tolerated, with very low incidence of ISRs
Zilucoplan PNH Phase 3 Pivotal Program – Study Design

- 2 global single-arm open-label multicenter studies, one study in treatment-naïve patients and a second, supportive study in eculizumab-switch patients; 6-month treatment period followed by a long term extension (LTE) study

### Naïve Patients (n=40 patients)

- **Patient Population:**
  - Naïve to complement inhibitor therapy
  - LDH ≥ 2xULN
  - Transfusion-Dependent, receiving at least one qualifying transfusion in the 6 months prior to screening

- **Dose:** 0.3mg/kg SC daily

- **Co-Primary Endpoints:**
  - Number of subjects achieving hemoglobin stabilization (relative to individual set point for each patient) and avoidance of any RBC transfusion over 6 months
  - Change in serum LDH from baseline to Month 6

### Switch Patients (n=40 patients)

- **Patient Population:**
  - Receiving eculizumab for at least 6 months prior to screening
  - No history of blood transfusions for at least 6 months prior to screening
  - Reticulocytes < 2xULN

- **Dose:** 0.3mg/kg SC daily

- **Primary Endpoint:**
  - Maintenance of transfusion-independence over 6 months
PNH Opportunity – Potential 1st Line Option to Treat All Naïve and Most Switch Patients

Prevalence: ~15.9 per million

Not Yet Diagnosed
~60%

Newly Diagnosed Per Year
~10%

On Treatment
~30%

60% Without EVH (transfusion independent and reticulocyte <2xULN)

40% With EVH (transfusion dependent)

Zilucoplan Opportunity

References:
Zilucoplan – Building a Pipeline within a Product

Expanded Market Opportunities Through Convenient Complement Control

Potential Future Indications
- ANCA Vasculitis
- Lupus Nephritis
- HELLP
- NMO
- TMA

Potential 1\textsuperscript{st} line option to urgently treat acute or progressive TMA

Potential 1\textsuperscript{st} line option to target complement-mediated damage earlier

Potential 1\textsuperscript{st} line option to treat all naive and most switch patients
**Generalized Myasthenia Gravis (gMG) – Rare, Debilitating, C5-Mediated Disease\(^1\)**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>~ 60,000 people in the US alone(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Antibodies block signals from nerves to muscles and complement activation destroys the neuromuscular junction(^3)</td>
</tr>
</tbody>
</table>
| Natural History | A rare disease, often overlooked\(^4\)  
• Commonly misdiagnosed; diagnosis can be delayed >5 years\(^4\)  
• ~80% of patients progress to generalized muscle weakness; ~20% experience crisis\(^5\) |
| Treatment | Sporadic, expensive, and often non-specific  
• Cholinesterase inhibitors, corticosteroids, immunosuppressants, thymectomy  
• Intravenous immunoglobulin (IVIg) and plasma exchange; Annual costs are ~$100,000\(^7\)  
• Eculizumab (Soliris\(^6\); Alexion), approved for gMG in 2017\(^7\); Annual costs are ~$700,000\(^9\) |
| Consequences | Serious and progressive  
• Systemic weakness significantly impacting quality of life\(^1,2\) |

**Autoantibodies and complement-mediated destruction of the neuromuscular junction cause pathology in gMG\(^1,2\)**

- **Normal**
  - Acetylcholine (Ach)
  - Acetylcholine receptor (AChR)
  - Muscle cell
  - Signal proceeds

- **Myasthenia Gravis**
  - Autoantibody that binds to AChr
  - Complement-mediated MAC assembly
  - Destruction of membrane

Zilucoplan in gMG – Opportunity to Target Complement-Mediated Damage Earlier

- MG Diagnosis
- Acetylcholinesterase Inhibitor
- Steroids
- Immunosuppressive Therapies
- IVIg/PLEX (Crisis or Chronic)
- Refractory

Thymectomy

Soliris (eculizumab) IV

IVIg = intravenous immunoglobulin
PLEX = plasmapheresis
Zilucoplan in gMG – Phase 2 Design

- Design: Randomized, double-blind placebo-controlled multicenter study, 12-week treatment period followed by a long term extension (LTE) study: Target enrollment n=36 patients

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

- Status:
  - Enrollment completed early (Aug. 2018); Enrollment target surpassed (n=44 patients)
  - Topline data read-out anticipated around year-end 2018
Zilucoplan in gMG – Phase 2 Design

Early Completion of Enrollment: 44 Patients (vs. target of 36)

- **Screening and Washout**
- **1:1:1 Randomization**
- **0.1 mg/kg SC**
- **0.3 mg/kg SC**
- **Placebo**
- **Anticipated top line data read-out around year-end 2018**
- **Long Term Extension (Active Drug)**
- **Study Period**
- **Long Term Extension**

- **Primary Efficacy Endpoint:** Change in QMG score from baseline to week 12
- **Secondary Endpoints include:** Myasthenia Gravis Activities of Daily Living (MG-ADL), Myasthenia Gravis Quality of Life (MG-QOL15r), Myasthenia Gravis Composite (MGC)
gMG Opportunity –
1st Line Option to Treat Complement-Mediated Damage Earlier

Prevalence: ~200 per million

- Controlled ~40%
- Uncontrolled ~40%
- Last Line ~20%

Patients adequately managed on steroids or Pyridostigmine

Patients lacking control despite treatments, including steroids and multiple ISTs.

Patients reverting to IVIg or plasmapheresis after trying earlier line treatments

Opportunity to serve up to ~60% of all patients with AChR+ gMG globally

References:
1. IQVIA market research sufficiency counts, May 4, 2018
2. IQVIA market research sufficiency counts, May 17, 2018.
Zilucoplan – Building a Pipeline within a Product

Expanded Market Opportunities Through Convenient Complement Control

- **Potential Future Indications**
  - ANCA Vasculitis
  - Lupus Nephritis
  - HELLP
  - NMO
  - TMA

Potential 1st line option to urgently treat acute or progressive TMA

Potential 1st line option to target complement-mediated damage earlier

Potential 1st line option to treat all naive and most switch patients
Zilucoplan Phase 1b PK Study in Renal Indications

Multi-center, Open-label Trial

8 patients with severe renal impairment

8 healthy control subjects with normal renal function

Each patient receives a single, SC dose of 0.3 mg/kg of RA101495 SC

PK profile in patients with renal impairment with subjects with normal renal function

Zilucoplan can be used in patients with renal impairment without any need for dose adjustment.
Zilucoplan Phase 1b PK Study in Renally Impaired Patients

- No difference in PK characteristics
- No dose adjustment required for renal indications
- No dose adjustment for PNH/gMG patients with reduced GFR
- No adverse events reported
Molecules bind to novel, cryptic site on C5 and prevent cleavage into C5a and C5b

- Block C5 activation by classical/lectin pathway and alternative pathway convertases
- Exhibit desirable drug-like properties (solubility, polar surface area, CLogP, etc.)

High potency and oral availability, favorable DMPK properties, and no adverse safety signals to date

SM Inhibits Complement Mediated Hemolysis of Human PNH Type III Erythrocytes in a Dose-Dependent Manner

Orally-Available, Small Molecule Inhibitors of C5
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 results in full blockade of ex-vivo zymosan-mediated C5 activation (incubation in whole blood)
Focused on rare hematologic, neurologic, and renal indications

Zilucoplan (RA101495 SC): Convenient, self-administered, subcutaneous C5 inhibitor
- Phase 3 studies in paroxysmal nocturnal hemoglobinuria (PNH) planned
- Phase 2 study in generalized myasthenia gravis (gMG):
  - Enrollment completed (ahead of schedule, Aug. 2018), target surpassed (n=44 pts vs. 36 pts)
  - Top line data read-out around year-end 2018
- Positive Phase 1b PK study in renally impaired patients; no dose adjustment required

Portfolio of C5 inhibitors in pre-clinical development
- Extended release formulation of zilucoplan
- First-in-class oral small molecule C5 inhibitor

Powerful proprietary drug discovery engine
- Trillion member, highly diverse, synthetic macrocyclic peptide libraries
- Diversity and specificity of mAbs with the pharmacologic advantages of small molecules

Collaboration with Merck for an oral peptide targeting a large CV market opportunity