Transforming Complement Therapeutics

June 2018
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Transforming Complement Therapeutics

- Focused on rare hematologic, renal, and neurologic indications

- RA101495 SC: Convenient, self-administered, subcutaneous C5 inhibitor
  - Phase 2 studies in paroxysmal nocturnal hemoglobinuria (PNH) completed
  - Phase 2 study in generalized myasthenia gravis (gMG) ongoing
  - Phase 1b PK study in renally impaired patients ongoing; Enrollment complete

- Portfolio of C5 inhibitors in pre-clinical development
  - Extended release formulation of RA101495 SC
  - 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

**Classical Pathway**
Activated by antibody-antigen complexes

**Lectin Pathway**
Activated by pathogen surfaces

**Multiple Indications**
- PNH: rupture of RBC
- gMG: destruction of neuromuscular junction
- aHUS: hemolytic anemia, thrombocytopenia, and renal failure
- LN: inflammation of kidney glomerulus

**Factors**
- C3
- C5
- C5a
- Proinflammatory cytokine
- Factor D, Factor B
- Factor H
- eculizumab
  - Binds C5
  - Binds C5 & C5b

**C5b-9 Activation**
- C5
  - C5b
  - C6
  - C7, C8, C9
  - Membrane attack complex (MAC)
### Pipeline Programs

#### C5 Inhibition Franchise

<table>
<thead>
<tr>
<th>Product</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA101495 SC (PNH)</td>
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<td></td>
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<tr>
<td>RA101495 SC (gMG)</td>
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<tr>
<td>RA101495 SC (renal; aHUS/LN)</td>
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<tr>
<td>RA101495 SC Extended Release (XR)</td>
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<tr>
<td>Oral Small Molecule Inhibitor</td>
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#### Factor D Inhibition

<table>
<thead>
<tr>
<th>Product</th>
<th>Phase 1</th>
</tr>
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<tbody>
<tr>
<td>Orphan Renal Diseases (SC)</td>
<td></td>
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</table>

#### Other Complement Inhibitors

<table>
<thead>
<tr>
<th>Product</th>
<th>Phase 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular/Autoimmune/CNS diseases</td>
<td></td>
</tr>
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</table>

#### Partnered Program

<table>
<thead>
<tr>
<th>Product</th>
<th>Phase 1</th>
</tr>
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<tbody>
<tr>
<td>Oral Macro cyclic Peptide</td>
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</table>
RA101495 SC – Positioned for Success

Large mAb (140 kDa) → Small Peptide (3 kDa)

Last Line → Earlier use

Long Infusion (~1 hr) → Brief Injection (5-8 sec.)

High Volume IV (90-120 mL) → Convenient SC (~0.5 mL)

Exclusive → Accessible

Rising Expectations for Complement Inhibition

Today → RA101495 SC
RA101495 SC – 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

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
Paroxysmal Nocturnal Hemoglobinuria (PNH) – Rare, Life-threatening, C5-Mediated Disease

| Frequency | ~ 8,000 to 10,000 people in North America and Europe
| 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

**RA101495 SC PNH Phase 2 – Study Design**

**Cohort A (naïve)**
- *n*=10

**Cohort B (switch)**
- *n*=16

**Inadequate Responders (LDH > 1.5 x ULN)**
- *n*=3

**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 is ≥ 1.5xULN, the dose is increased to 0.3mg/kg SC once daily
RA101495 SC in Treatment Naïve PNH – Rapid, Robust, Sustained Reduction of LDH

Dose Dependence of Complement Inhibition

Comparable LDH Reduction to Eculizumab\(^1,2\)

**Relative overdosing of eculizumab during weekly loading period coincides with relative underdosing of RA101495 during dose-titration**

*Not a head-to-head comparison.

**Weekly eculizumab loading period**

RA101495 SC in Treatment Naïve PNH – Treatment Satisfaction and Transfusion Improvements

Treatment Satisfaction Score
Mean (SE), n=19

- Very Satisfied: 5
- Satisfied: 4
- Neutral: 3
- Dissatisfied: 2
- Very Dissatisfied: 1

At final study visit (W12)

Improvements in Transfusion Dependence

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Transfused during 6 months prior to Week 0 visit</th>
<th>Transfused anytime after Week 0 visit while on study*</th>
</tr>
</thead>
<tbody>
<tr>
<td>007-001</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>007-002</td>
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<td>014-001</td>
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<td>017-002</td>
<td>Yes</td>
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</table>

50% of treatment naïve, transfusion-dependent patients have been transfusion-free while on RA101495 SC
RA101495 SC in Eculizumab Switch – Success in Defined Sub-Population

Robust LDH Control in Transfusion-Independent Patients

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

LDH (U/L)

Week

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

0 500 1000 1500

1.5x ULN

Transfusion Dependent

Transfusion Independent

n= 11

n= 5

10 9 7 6 4 2 1 1 7 early withdrawals

5 5 4 4 4 2 2 2 1 early withdrawal

0.0

0.1

0.2

0.3

0.4

0.5

Reticulocyte Count x10^6/L

Baseline (Week 0)

Switch Successes

Switch Failures

2xULN

ULN
RA101495 SC Phase 2 PNH Program – Safety and Tolerability

- Cumulative RA101495 SC exposure: Over 700 patient-weeks
- 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
- 9 mild (grade 1) ISRs among 5 subjects out of >5,000 self-administered injections
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)

References:
RA101495 SC – Building a Pipeline within a Product

Expanded Market Opportunities Through Convenient Complement Control

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

**Development**
- Ph1
- Ph2

**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 naïve and most switch patients

**PNH**
**gMG**
**aHUS**
Generalized Myasthenia Gravis (gMG) – Rare, Debilitating, C5-Mediated Disease

<table>
<thead>
<tr>
<th>Frequency</th>
<th>~ 60,000 people in the US alone²</th>
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<tbody>
<tr>
<td>Cause</td>
<td>Antibodies block signals from nerves to muscles and complement activation destroys the neuromuscular junction³</td>
</tr>
<tr>
<td>Natural History</td>
<td>A rare disease, often overlooked⁴</td>
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<td></td>
<td>▪ Commonly misdiagnosed; diagnosis can be delayed &gt;5 years⁴</td>
</tr>
<tr>
<td></td>
<td>▪ ~80% of patients progress to generalized muscle weakness⁵; ~20% experience crisis⁶</td>
</tr>
<tr>
<td>Treatment</td>
<td>Sporadic, expensive, and often non-specific</td>
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<tr>
<td></td>
<td>▪ Cholinesterase inhibitors, corticosteroids, immunosuppressants, thymectomy</td>
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<td></td>
<td>▪ Intravenous immunoglobulin (IVIg) and plasma exchange; Annual costs are ~$100,000⁷</td>
</tr>
<tr>
<td></td>
<td>▪ Eculizumab (Soliris⁸; Alexion), approved for gMG in 2017⁹; Annual costs are ~$700,000⁹</td>
</tr>
<tr>
<td>Consequences</td>
<td>Serious and progressive</td>
</tr>
<tr>
<td></td>
<td>▪ Systemic weakness significantly impacting quality of life¹,²</td>
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</tbody>
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Autoantibodies and complement-mediated destruction of the neuromuscular junction cause pathology in gMG¹,²

RA101495 SC in gMG – Opportunity to Target Complement-Mediated Damage Earlier

MG Diagnosis → Acetylcholinesterase Inhibitor → Steroids → Immunosuppressive Therapies → IVlg/PLEX (Crisis or Chronic) → Refractory

RA101495 SC Opportunity

- Thymectomy
- Soliris (eculizumab) IV

IVlg = intravenous immunoglobulin
PLEX = plasmapheresis
RA101495 SC 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

**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
19 Patients Dosed as of June 5, 2018

- **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 –
Potential 1st Line Option to Treat Complement-Mediated Damage Earlier

Prevalence: ~200 per million

- Patients adequately managed on **steroids** or **Pyridostigmine**
  - Controlled: ~40%
- Patients lacking control despite treatments, including **steroids and multiple ISTs**.
  - Uncontrolled: ~40%
- Patients reverting to **IVIg or plasmapheresis** after trying earlier line treatments
  - Last Line: ~20%

References:
1. IQVIA market research sufficiency counts, May 4, 2018.
2. IQVIA market research sufficiency counts, May 17, 2018.
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Potential 1st line option to treat all naive and most switch patients
Atypical Hemolytic Uremic Syndrome (aHUS) – Rare, Life-threatening, C5-Mediated Disease

**Frequency**
~ 2 cases per million worldwide¹

**Cause**
Uncontrolled fluid phase activation of complement that results in formation of blood clots in small blood vessels throughout the body²,³

**Diagnosis**
Ultra rare, frequently not recognized²⁻⁴
- In 70% of patients, aHUS onset was associated with a triggering event, such as infection⁴,⁵
- ~60% are children (<18 years of age)

**Treatment**
Expensive and often imperfect
- Plasma infusion or exchange, dialysis, kidney transplant⁶
- Eculizumab (Soliris®; Alexion) is the first FDA-approved treatment for aHUS⁷

**Consequences**
Severe and life-threatening
- Kidney failure, stroke, heart attacks, seizures and high blood pressure⁸

Historically, despite management, within 3 years of diagnosis 79% of patients required dialysis, had permanent kidney damage, or died.³

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**References:**
Phase 1b PK Study in Renal Indications

Multi-center, Open-label Trial
Data Expected Mid-2018

8 patients with severe renal impairment

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

8 healthy control subjects with normal renal function

Trial will compare the PK profile in patients with renal impairment with subjects with normal renal function

Enrollment Recently Completed
Orally-Available, Small Molecule Inhibitors of C5

- 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**

Podium presentation at EHA 23 (Stockholm)
Alonso Ricardo, Ph.D.
Sunday, June 17, 8:15-8:30 CEST
Room A8; Abstract Code: 3854
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