Complement Immunotherapy using compstatin derivatives
Complement system plays key role in wide range of autoimmune and inflammatory diseases

**Lead Indications**

- Paroxysmal nocturnal hemoglobinuria (PNH)
- Refractory Myasthenia Gravis
- Neuromyelitis Optica
- Intermediate AMD
- Geographic Atrophy in AMD
- COPD

**Secondary Indications**

- Chronic Obstructive Pulmonary Disease (COPD)
- Idiopathic Pulmonary Fibrosis
- Refractory Myasthenia Gravis
- Chronic Kidney Rejection
APL-1 and APL-2, compstatin derivatives

APL-1 (short-acting) and APL-2 (long-acting) are potent and selective peptide C3 inhibitors

▸ APL-1
  ▪ Nebulized for COPD

▸ APL-2
  ▪ Long-acting versions of APL-1
  ▪ Subcutaneous for PNH
  ▪ Intravitreal for AMD
Unmet need in paroxysmal nocturnal hemoglobinuria

DISEASE
- ~4,700 patients in the US
- Severe anemia, thrombotic risk, impaired bone marrow functions
- ~35% 5-year mortality if left untreated (main cause: thrombosis)

STANDARD OF CARE
- Soliris® only approved therapy
  - Controls intravascular hemolysis
  - ~$583,000 / year / adult patient

UNMET NEED
- 35-40% of patients on Soliris continued to be transfusion-dependent for 30 months following the beginning of treatment*
  - Soliris® does not prevent C3b-mediated extravascular hemolysis
- Soliris® has inconvenient bi-weekly IV dosing

35-40% of Soliris patients continue to be transfusion dependent*

(Dr. Hillmen is an advisor to Apellis)
Inhibition of C5 prevents C5a and MAC but not C3a-mediated inflammation and C3b deposition

**Activation Pathways**
- **Classical pathway** Activated by antibody-antigen complex
- **Lectin pathway** Activated by lectin and mannose complex
- **Alternative pathway** Spontaneous C3 convertase activation

**C3**
- **C3a**
- **C3b**

**Inflammation**
- C3b on RBC

**C5**
- **C5a**
- **C5b MAC**

**Inflammation**
- Eculizumab

**Intravascular**
- Extravascular
Broader inhibition of complement at C3 may overcome limitations of C5 inhibition

Potential Benefits APL-2
- Prevention of blood clot formation
- Reduced anemia and transfusion dependency
- Ease of use (self-administered once daily)
- Disease modifying potential
Evidence of effectiveness of C3 inhibition

Abstract at ASH Conference 2013 by Dr. Peter Hillmen, Leeds Teaching Hospitals, NHS Trust, United Kingdom (Dr. Hillmen is an advisor to Apellis)
Evidence of safety of C3 inhibition

- A small population of individuals lack functional levels of C3 and C5*
- These individuals are susceptible to infection by certain bacterial species

**C5-deficient individuals**
- Neisseria *meningitidis*

**C3-deficient individuals**
- Neisseria *meningitidis*, Streptococcus *pneumoniae*, Haemophilus *influenzae*

**INFECTION RISK MANAGEABLE WITH VACCINATION**

- No cases of drug-related infections following experiments involving >300 non-human primates
  - Multiple compounds (APL-1, APL-2 and others)
  - Acute and chronic exposure
- No cases of infections with subcutaneous APL-2 to date – triple vaccination
- No cases of infections with intravitreal APL-2 to date – no vaccination
- Two cases of fever with nebulized APL-1 (resolved with antibiotics) – single vaccination

## Phase 1 Studies

Design: randomized, double-blind, placebo-controlled, single and multiple ascending dose studies to assess the safety, tolerability, PK and PD of subcutaneous APL-2 in healthy adult subjects who have received the triple vaccination.

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Doses &amp; dosing period</th>
<th>Endpoints</th>
<th>Preliminary Results</th>
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<td>Phase 1 Healthy SAD</td>
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<td>• Safety/tolerability</td>
<td>No SAEs. Well tolerated</td>
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<td>Reduced hemolytic activity</td>
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<td>Phase 1 Healthy MAD</td>
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<td>16 active</td>
<td>• 30 – 270 mg/day</td>
<td>• PK/PD</td>
<td>Dose-dependent increase of C3</td>
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<tr>
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<td>4 placebo</td>
<td>• 28 days</td>
<td>• Hemolytic activity</td>
<td>Reduced hemolytic activity</td>
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</tbody>
</table>
HV / 28-day MD summary PK

Nominal time post first dose (days)

APL-2 concentration (ug/mL)

- CP1014: 270 mg/day
- CP1014: 180 mg/day
- CP1014: 90 mg/day
- CP1014: 30 mg/day
Complement-APL-2 binding: C3 increase

Mean Serum C3 Concentrations Over Time
Normal hemolytic activity in placebo subject

Hemolysis of Red Blood Cells by the Alternative Pathway
(1:4 Plasma Dilution)

- Healthy Subject (placebo)

- Up to 96% knockdown of C5 with Alnylam’s ALN-CC5 gives max 61% inhibition of hemolytic activity*,***

- Effective complement inhibition by Soliris (≤20% hemolytic activity)**,***

*** Hemolytic activity assays used may vary
APL-2 reduces hemolytic activity (cohort 3, 180 mg)

Hemolysis of Red Blood Cells by the Alternative Pathway

Effective complement inhibition by Soliris (≤20% hemolytic activity)**,***

*** Hemolytic activity assays used may vary
APL-2 reduces hemolytic activity (cohort 4, 270 mg)
Phase 1b studies in PNH patients

To assess the safety, preliminary efficacy and pharmacokinetics of subcutaneously administered APL-2

The Paddock study
- Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH) that have not been treated with Eculizumab in the past
- Total of 6 subjects in 2 Cohorts
- Two doses: 180 and 270 mg/d of APL-2 for 28 days

The Pharoah study
- Subjects with PNH currently receiving Eculizumab
- Total of 8 subjects in 4 Cohorts
- Doses ranging for 30mg/d to 270 mg/d of APL-2 for 28 days

Both Studies
- **Primary Endpoints**: number and severity of TEAEs and pharmacokinetics parameters of APL-2 following administration of multiple SC doses
- **Secondary Endpoints**: Lactate dehydrogenase (LD), Hemoglobin, Haptoglobin, PNH clones
Conclusion of the phase 1 studies

- C3 inhibition can be achieved
- APL-2 was safe and well-tolerated
- APL-2’s PK/PD profile supports daily subcutaneous administration
- APL-2 significantly reduced the hemolytic activity