A Subcutaneously Administered Investigational RNAi Therapeutic (ALN-CC5) Targeting Complement C5 for Treatment of PNH and Complement-Mediated Diseases: Interim Phase 1 Study Results

22 May 2016
ERA-EDTA
ALN-CC5 and Complement-Mediated Diseases

Excessive complement activity drives disease pathophysiology in many indications
• Paroxysmal nocturnal hemoglobinuria (PNH)
• Atypical hemolytic uremic syndrome (aHUS)
• Neuromyelitis optica (NMO)
• Myasthenia gravis (MG)
• Many others

Complement C5 is a genetically validated target
• Human C5 deficiency associated with minimal complications
  ◦ Increased susceptibility to Neisseria infections

Complement C5 is a clinically validated target
• Eculizumab is an anti-C5 mAb
  ◦ Approved for use in patients with PNH and aHUS
Complement-Mediated Diseases Addressed by C5 Blockade – PNH and aHUS

Paroxysmal Nocturnal Hemoglobinuria (PNH) Background
- Bone marrow defect due to acquired PIG-A gene mutation leading to deficiency of GPI-anchored surface proteins that protect red blood cells against complement mediated cell lysis
- Concomitant quantitative bone marrow failure in ~50% of patients with anemia and increased risk of infection
- Life threatening complications include:
  ◦ Arterial or venous thromboembolism
  ◦ Kidney failure
  ◦ Pulmonary hypertension
- Risk of complications highest during inflammation
- Eculizumab is a monoclonal antibody targeting C5 approved for treatment of PNH¹

Atypical Hemolytic Uremic Syndrome (aHUS) Background
- Rare disease causing uncontrolled activation of the alternative complement pathway by genetic mutations affecting complement regulators or by the acquired development of complement factor autoantibodies
- Leading to damage of systemic endothelial beds, platelet activation and thrombotic microangiopathy
- Life threatening complications include:
  ◦ End stage renal disease
  ◦ Extra-renal organ damage
- Eculizumab is a monoclonal antibody targeting C5 approved for treatment of aHUS¹

¹Soliris® [package insert]. New Haven, CT; Alexion Pharmaceuticals Inc; revised 2016.
Current PNH Treatment Challenges

Poor Responders, Breakthrough Hemolysis & C5 Fluctuations

• Eculizumab is potent inhibitor of C5, however significant proportion of PNH patients experience breakthrough or occult hemolysis\(^1\)
• Complement C5 is an acute phase protein and inflammation causes C5 fluctuations of up to ~100%\(^2\)
• Wide inter-individual variation in pharmacodynamics and clearance of eculizumab\(^3\-4\)

Unmet need exists for new therapeutic options

• Consistent level of efficacy
  ◦ LDH <1.5 x ULN determined to result in improved patient outcomes\(^5\,6\)
• SC delivery for more tolerable treatment regimen

ALN-CC5: SC-Administered GalNAc-Conjugated siRNA Targeting C5

ALN-CC5

- siRNA conjugated to N-acetylgalactosamine (GalNAc) ligand
- Efficient delivery to hepatocytes following subcutaneous (SC) administration
- Wide therapeutic index
- Utilizes enhanced stabilization chemistry (ESC)
  - Significantly improved potency and durability

Recognition of GalNAc ligand by asialoglycoprotein receptor (ASGPR)

- Highly expressed in hepatocytes
- High rate of uptake
- Recycling time ~15 minutes
- Conserved across species
ALN-CC5 Phase 1/2 Study Design
Healthy Volunteers and Patients with PNH

Part A: Single-Ascending Dose (SAD): Healthy Volunteers
Randomized 3:1, double blind, placebo controlled, N=4/cohort

- 50 mg x 1 SC: dosing completed
- 200 mg x 1 SC
- 400 mg x 1 SC
- 600 mg x 1 SC
- 900 mg x 1 SC

Part B: Multiple-Ascending Dose (MAD): Healthy Volunteers
Randomized 3:1, Double blind, Placebo controlled, N=4/cohort

- 100 mg qW x 5 SC: dosing completed
- 200 mg qW x 5 SC
- 400 mg qW x 5 SC
- 600 mg q2W x 7 SC
- 200 mg qW x 5, q2W x 4 SC
- 200 mg qW x 5, qM x 2 SC

Part C: Multiple Dose (MD): Patients with PNH
Open label, N ~ 5

ALN-CC5 dosed subcutaneously as a 200 mg/mL solution

Ongoing
Materials and Methods

Pharmacodynamic (PD) assays

- Serum concentrations of C5 assayed using validated LCMS assay
- Complement activity
  - Serum samples assessed using CAP and CCP Wieslab® ELISA assays (alternative and classical pathways, respectively)
  - Serum samples assessed using in-house sheep erythrocyte hemolysis assay and CH50 assay (both exploratory)

Data from Phase 1/2 Part A (SAD) and Part B (MAD)

- Part A: Double blind safety and tolerability single ascending dose (SAD) study of ALN-CC5 in healthy volunteers (20) randomized 3:1 (ALN-CC5:placebo)
- Part B: Double blind safety and tolerability multiple ascending dose (MAD) study of ALN-CC5 in healthy volunteers (24) randomized 3:1 (ALN-CC5:placebo)

Results preliminary as study is ongoing
## Demographics and Baseline Characteristics

**44 healthy volunteers dosed with ALN-CC5 or placebo (3:1)**

<table>
<thead>
<tr>
<th></th>
<th>Part A: Single Ascending Dose (SAD)</th>
<th>Part B: Multiple Ascending Dose (MAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=4/cohort</td>
<td>N=4/cohort</td>
</tr>
<tr>
<td>Age (years), Mean (Min, Max)</td>
<td>50 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Age (years), Mean (Min, Max)</td>
<td>23.8 (20, 26)</td>
<td>22.5 (21, 24)</td>
</tr>
<tr>
<td>Gender: Male (%)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>BMI (kg/m²), Mean</td>
<td>24.08</td>
<td>22.35</td>
</tr>
<tr>
<td>Race (%)</td>
<td>- Asian</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>- Black/African</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>- Caucasian</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>- Other</td>
<td>25%</td>
</tr>
<tr>
<td>Time on study, Mean (days)</td>
<td>115</td>
<td>286</td>
</tr>
</tbody>
</table>

*Data transfer: 03/02/2016*

This is a double-blinded study; each cohort above remains blinded with one placebo per cohort.
ALN-CC5 Phase 1/2: Part A – SAD*
Blinded Safety and Tolerability Summary

**ALN-CC5 was generally well tolerated in healthy volunteers**

- No SAEs and no discontinuation due to adverse events (AE)
- 14 healthy volunteers (70%) reported at least one AE; all were mild or moderate
  - 2 healthy volunteers (10%) reported at least one possibly related AE; all were mild
    - Nasopharyngitis (n=1), injection site pain/rash (n=1)
  - 2 healthy volunteers (10%) reported injection site reactions (ISR); all were mild
    - Injection site pain and/or rash
- No clinically significant changes in vital signs, EKG, physical exams and clinical laboratories (hematology, biochemistry, coagulation and urinalysis)

**Adverse Events (AEs) reported in ≥10% of healthy volunteers**

<table>
<thead>
<tr>
<th>AE by Preferred Term</th>
<th>50 mg</th>
<th>200 mg</th>
<th>400 mg</th>
<th>600 mg</th>
<th>900 mg</th>
<th>All dosing Cohorts N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>
ALN-CC5 Phase 1/2: Part B – MAD*
Blinded Safety and Tolerability Summary

ALN-CC5 was generally well tolerated in healthy volunteers

- No SAEs and no discontinuation due to adverse events (AE)
- 19 healthy volunteers (79%) reported at least one AE; all were mild or moderate
  - 10 healthy volunteers (42%) reported at least one possibly related AE; all were mild or moderate
    - Nasopharyngitis (n=4); aphthous stomatitis, contusion, fatigue, headache, injection site (IS) bruising, IS edema, IS erythema, IS pruritus, IS rash, insomnia, nausea, and vulvovaginal candidiasis (n=1/each)
  - 4 healthy volunteers (17%) reported injection site reactions (ISR); all were mild
    - Bruising, erythema, edema, pruritus and/or rash at the injection site (n=1/each)

- No clinically significant changes in vital signs, EKG, physical exams and clinical laboratories (hematology, biochemistry, coagulation and urinalysis)

### Adverse Events (AEs) reported in ≥10% of healthy volunteers

<table>
<thead>
<tr>
<th>AE by Preferred Term</th>
<th>100 mg qW x 5</th>
<th>200 mg qW x 5</th>
<th>400 mg qW x 5</th>
<th>600 mg q2W x 7</th>
<th>200 mg qW x 5, q2W x 4</th>
<th>200 mg qW x 5, qM x 2</th>
<th>All dosing cohorts N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4 (17%)</td>
</tr>
</tbody>
</table>

*Data transfer: 3/2/2016*
ALN-CC5 Phase 1/2: Part A – SAD*
Pharmacodynamics and Clinical Activity: Serum C5

**Serum C5 knockdown following single dose of ALN-CC5**

- Maximum C5 knockdown relative to baseline up to 99%
- Mean maximum (± SEM) C5 knockdown: 98 ± 0.9% (600 mg)
- Mean (± SEM) C5 knockdown:
  - Day 98 (600 mg): 97 ± 1.1%
  - Day 182 (600 mg): 94 ± 1.2%
ALN-CC5 Phase 1/2: Part A – SAD*
Summary of Preliminary Results

<table>
<thead>
<tr>
<th>Residual C5</th>
<th>Part A: Single Ascending Dose (SAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single subcutaneous injection</td>
</tr>
<tr>
<td></td>
<td>50 mg</td>
</tr>
<tr>
<td>Residual C5</td>
<td></td>
</tr>
<tr>
<td>Mean nadir; mcg/mL ± SEM</td>
<td>15.3 ± 2.5</td>
</tr>
<tr>
<td>Nadir; mcg/mL</td>
<td>10.8</td>
</tr>
<tr>
<td>C5 knockdown</td>
<td></td>
</tr>
<tr>
<td>Mean max; % ± SEM</td>
<td>78 ± 3.2</td>
</tr>
<tr>
<td>Max; %</td>
<td>84</td>
</tr>
<tr>
<td>CAP inhibition</td>
<td></td>
</tr>
<tr>
<td>Mean max; % ± SEM</td>
<td>59 ± 7.3</td>
</tr>
<tr>
<td>Max; %</td>
<td>73</td>
</tr>
<tr>
<td>CCP inhibition</td>
<td></td>
</tr>
<tr>
<td>Mean max; % ± SEM</td>
<td>59 ± 6.5</td>
</tr>
<tr>
<td>Max; %</td>
<td>72</td>
</tr>
<tr>
<td>Hemolysis inhibition</td>
<td></td>
</tr>
<tr>
<td>Mean max; % ± SEM</td>
<td>35 ± 7.9</td>
</tr>
<tr>
<td>Max; %</td>
<td>51</td>
</tr>
</tbody>
</table>

*Data transfer: 03/02/2016 for C5, CAP, CCP; data transfer: 03/14/2016 for hemolysis inhibition
ALN-CC5 Phase 1/2: Part B – MAD*
Pharmacodynamics and Clinical Activity: Serum C5

Serum C5 knockdown following multiple doses of ALN-CC5
• Maximum C5 knockdown relative to baseline up to 99%
• Mean maximum (± SEM) C5 knockdown: 99 ± 0.2% (600 mg, q2W ×7)
• Mean (± SEM) C5 knockdown: 99 ± 0.2% at Day 112 (600 mg, q2W ×7)

*Data transfer: 03/02/2016
ALN-CC5 Phase 1/2: Part B – MAD* Pharmacodynamics and Clinical Activity: CAP

Complement Alternative Pathway inhibition (CAP C5b-9 ELISA)

- Multiple doses of ALN-CC5
- Maximum CAP inhibition relative to baseline up to 99.5%
- Mean maximum (± SEM) CAP inhibition: 97 ± 1.5% (400 mg, qW ×5)
- CAP activity comparable to homozygous C5 deficient subjects¹ in 200mg cohort and above

![Graph showing CAP reduction over time with different dosing regimens.]

Complement Classical Pathway inhibition (CCP C5b-9 ELISA)

- Multiple doses of ALN-CC5
- Maximum CCP inhibition relative to baseline up to 99.4%
- Mean maximum (± SEM) CCP inhibition: 97.3 ± 1.0% (400 mg qW ×5)
- CCP activity comparable to homozygous C5 deficient subjects\(^1\) in 200mg cohort and above

Inhibition of sheep erythrocyte hemolysis

- Multiple doses of ALN-CC5
- Maximum serum hemolysis inhibition relative to baseline up to 98%
- Mean maximum (± SEM) serum hemolysis inhibition: 86 ± 1.5% (600 mg q2W ×7)
ALN-CC5 Phase 1/2: Part B – MAD*
Pharmacodynamics and Clinical Activity: CH50

Reduction of CH50 activity
- Multiple doses of ALN-CC5
- Maximum CH50 inhibition relative to baseline up to 100%
- Mean maximum (± SEM) CH50 inhibition: 99.6 ± 0.2% (200mg, qW ×5)
## ALN-CC5 Phase 1/2: Part B – MAD*

### Summary of Preliminary Results

#### Part B: Multiple Ascending Dose (MAD) - Multiple Subcutaneous Injections

<table>
<thead>
<tr>
<th>Dose</th>
<th>100 mg qW x 5</th>
<th>200 mg qW x 5</th>
<th>400 mg qW x 5</th>
<th>600 mg q2W x 7</th>
<th>200 mg qW x 5, q2W x 4</th>
<th>200 mg qW x 5, qM x 2</th>
<th>Placebo N=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual C5 levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean nadir; mcg/mL ± SEM</td>
<td>4.2 ± 0.5</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.2</td>
<td>0.8 ± 0.1</td>
<td>1.4 ± 0.3</td>
<td>2.7 ± 1.7</td>
<td>60.2 ± 5.4</td>
</tr>
<tr>
<td>Nadir; mcg/mL</td>
<td>3.5</td>
<td>0.6</td>
<td>1.0</td>
<td>0.7</td>
<td>1.0</td>
<td>1.0</td>
<td>37.3</td>
</tr>
<tr>
<td>C5 knockdown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean max; % ± SEM</td>
<td>95 ± 0.4</td>
<td>98 ± 0.5</td>
<td>98 ± 0.2</td>
<td>99 ± 0.2</td>
<td>98 ± 0.4</td>
<td>97 ± 2.1</td>
<td>24 ± 5.3</td>
</tr>
<tr>
<td>Max; %</td>
<td>96</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>43</td>
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<tr>
<td>CAP inhibition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean max; % ± SEM</td>
<td>84 ± 2.1</td>
<td>95 ± 1.0</td>
<td>97 ± 1.5</td>
<td>97 ± 0.8</td>
<td>95 ± 0.8</td>
<td>89 ± 6.5</td>
<td>25 ± 5.8</td>
</tr>
<tr>
<td>Max; %</td>
<td>88</td>
<td>97</td>
<td>100</td>
<td>98</td>
<td>96</td>
<td>96</td>
<td>50</td>
</tr>
<tr>
<td>CCP inhibition</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean max; % ± SEM</td>
<td>85 ± 2.6</td>
<td>96 ± 0.9</td>
<td>97 ± 1.0</td>
<td>97 ± 0.7</td>
<td>96 ± 1.0</td>
<td>89 ± 6.0</td>
<td>28 ± 7.0</td>
</tr>
<tr>
<td>Max; %</td>
<td>91</td>
<td>97</td>
<td>99</td>
<td>98</td>
<td>98</td>
<td>95</td>
<td>50</td>
</tr>
<tr>
<td>Hemolysis inhibition†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean max; % ± SEM</td>
<td>52 ± 4.9</td>
<td>75 ± 8.0</td>
<td>84 ± 7.6</td>
<td>86 ± 1.5</td>
<td>--</td>
<td>--</td>
<td>5 ± 2.0</td>
</tr>
<tr>
<td>Max; %</td>
<td>58</td>
<td>91</td>
<td>98</td>
<td>89</td>
<td>--</td>
<td>--</td>
<td>10</td>
</tr>
</tbody>
</table>

*Data transfer: 03/02/2016 for C5, CAP, CCP; data transfer: 03/14/2016 for hemolysis inhibition; †N=4 for placebo group
-- Not assessed
ALN-CC5 Phase 1/2 Study Results*
Summary and Next Steps

- ALN-CC5 represents a novel investigational approach for the potential treatment of PNH and other complement-mediated diseases, such as aHUS
- In an ongoing Phase 1/2 study in healthy volunteers (N=44), single and multi-dose subcutaneous administration of ALN-CC5 is generally well tolerated
  - No reported SAEs; all AEs mild or moderate; no discontinuations; low incidence of mild injection site reactions (ISRs)
- Robust, dose-dependent and durable KD of serum C5
  - After single dose, up to 99% C5 KD with mean max KD of 98 ± 0.9% (600mg)
  - After multiple doses, up to 99% C5 KD with mean max KD of 99 ± 0.2% (600 mg, q2W ×7)
  - Clamped lowering of C5 with very low inter-subject variability
  - Durable KD and complement inhibition lasting months, supportive of once monthly and potentially once quarterly SC dose regimen
- Assessment of ALN-CC5 in PNH patients (Part C) ongoing
- Broad development plan to address multiple complement-mediated diseases
  - Phase 2 in PNH focused on eculizumab poor responders and for eculizumab sparing expected to start by end of 2016
  - Additional studies in other complement-mediated disease indications such as aHUS and myasthenia gravis expected to start in early 2017
## Acknowledgements

### Trial participants

#### Principal investigators

<table>
<thead>
<tr>
<th>Country</th>
<th>PI Name</th>
<th>Location</th>
</tr>
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<tbody>
<tr>
<td>United Kingdom</td>
<td>Jorg Taubel</td>
<td>Richmond Pharmacology Ltd, Tooting, UK</td>
</tr>
<tr>
<td></td>
<td>Jim Bush</td>
<td>Covance Clinical Research Unit Limited, Leeds, UK</td>
</tr>
<tr>
<td></td>
<td>Anita Hill</td>
<td>Department of Haematology, Leeds Teaching Hospitals, Leeds, UK</td>
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<td>Spain</td>
<td>Alvaro Urbana-Ispizua</td>
<td>Department of Hematology, Hospital Clinic, University of Barcelona, Barcelona, Spain</td>
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Thank You