A Subcutaneously Administered Investigational RNAi Therapeutic (ALN-CC5) Targeting Complement C5 for Treatment of PNH and Complement-Mediated Diseases: Interim Phase 1/2 Study Results

June 11th, 2016 | EHA 2016 | Copenhagen
Paroxysmal Nocturnal Hemoglobinuria (PNH)

Background
• Bone marrow defect due to acquired PIG-A gene mutation
  ◦ Leads to deficiency of glycoporphosphatidylinositol (GPI)-anchored surface proteins that protect red blood cells against complement-mediated cell lysis
• Concomitant 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 (Ecu) is a monoclonal antibody targeting C5 approved for treatment of PNH and aHUS

Current treatment challenges
• Complement C5 is acute phase protein and inflammation causes C5 fluctuations of up to ~100%\(^1\)
• Considerable proportion of PNH patients on Ecu experience breakthrough hemolysis\(^2\)
• Wide inter-individual variation in pharmacodynamics and clearance of Ecu\(^2-4\)
• Discrepancy between Ecu’s labeled effective trough level of 35 mcg/mL (ref label) versus expert recommendations of at least 150 mcg/mL\(^2\)
• QoL and economic burden associated with need for frequent Ecu IV infusions

Unmet need for new complement inhibitors remains

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**ALN-CC5 and Study Rationale**

**ALN-CC5 is an investigational RNAi therapeutic targeting C5**
- siRNA conjugated to N-acetylgalactosamine (GalNAc) ligand
- Efficient delivery to hepatocytes following subcutaneous (SC) administration
- Potential application in a broad range of complement-mediated diseases
- Ongoing Phase 1/2 study conducted in healthy volunteers (Parts A and B), N=56
  - Generally well tolerated following single and multiple doses
  - Potent knockdown (KD) of serum C5 and inhibition of complement activity
  - Highly durable effects with >90% serum C5 knockdown at 6 months after single dose

**In Part C of study, exploratory evaluation of ALN-CC5 and hepatic C5 knockdown for the treatment of PNH**
- ALN-CC5 clinical activity studied as monotherapy or as adjunct to Ecu
  - Eligible patients included those who are Ecu naïve or on background Ecu, including patients with inadequate response to Ecu
- Conducted exploratory analysis of potential for reducing dose and frequency of Ecu
ALN-CC5 Phase 1/2 Study - Part C
Patients with PNH – Ecu Naïve and on Background Ecu

Part C: Multiple Dose (MD): Patients with PNH | Open label, N = 6

Ecu naïve

- Patient 0081
- Patient 0082
- Patient 0061

Background Ecu

- Patient 0063
- Patient 0064
- Patient 0083

Primary objectives:
- Safety, tolerability

Secondary objectives:
- PK, C5, LDH
- Complement activity assessment

ALN-CC5 dosed subcutaneously in 200 mg/mL solution
6 Patients with PNH administered ALN-CC5

<table>
<thead>
<tr>
<th>Part C : PNH Patients</th>
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<tbody>
<tr>
<td>Age (years), Mean (Min, Max)</td>
<td>43.7 (25, 58)</td>
</tr>
<tr>
<td>Gender: Male(%)</td>
<td>50%</td>
</tr>
<tr>
<td>BMI (kg/m²), Mean</td>
<td>24.6</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
</tr>
<tr>
<td>- Asian</td>
<td>0%</td>
</tr>
<tr>
<td>- Black/African</td>
<td>0%</td>
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<tr>
<td>- Caucasian</td>
<td>100%</td>
</tr>
<tr>
<td>- Other</td>
<td>0%</td>
</tr>
<tr>
<td>Time on study, Mean (days)</td>
<td>81</td>
</tr>
</tbody>
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*Based on data transferred up to 06June2016
Initial ALN-CC5 Phase 1/2 Part C Study Results*
Safety and Tolerability Summary

ALN-CC5 is generally well tolerated in patients with PNH after multiple doses

- No SAEs or discontinuations due to adverse events (AEs)
- All 6 patients reported at least one AE
  - Majority of AEs were mild to moderate in severity
  - 1 severe AE reported as hepatotoxicity
    - Asymptomatic, transient grade 3 elevation of ALT and AST without increase in total bilirubin
    - Event considered possibly related to study drug resulting in dose interruption
    - Other concomitant medications suspended (cyclosporine and anabolic steroid)
  - AEs reported in ≥ 2 patients: contusion, oropharyngeal pain (N=2 each)
  - 4 patients reported at least one possibly or definitely related AE
    - Hepatotoxicity (N=1, listed above)
    - Mild injection site reactions (ISRs) reported in 3 patients
      » Contusion (N=2), listed above; erythema and pain (N=1)
- No other clinically significant changes in vital signs, EKG, physical exams or clinical laboratories (hematology, biochemistry, coagulation and urinalysis)

*Based on data transferred up to 06June2016
ALN-CC5 Phase 1/2 Study - Part C
Patients with PNH – Ecu Naïve and on Background Ecu

Part C: Multiple Dose (MD): Patients with PNH
Open label, N = 6

- **Ecu naïve**
  - Patient 0081
    - 200 mg qW x 13, 400 mg qW x 4 SC
  - Patient 0082
    - 200 mg qW x 13, 400 mg qW x 4 SC
  - Patient 0061
    - 400 mg qW x 8 SC

- **Background Ecu**
  - Patient 0063
    - 900 mg Ecu q2W
  - Patient 0064
    - 900 mg Ecu q2W
  - Patient 0083
    - 1200 mg Ecu q2W
    - Ecu inadequate responder

**Primary objectives:**
- Safety, tolerability

**Secondary objectives:**
- PK, C5, LDH
- Complement activity assessment

ALN-CC5 dosed subcutaneously in 200 mg/mL solution
Initial ALN-CC5 Phase 1/2 Part C Study Results*
C5 KD and Complement Inhibition in Ecu Naïve Patients

Serum C5 KD following multiple doses of ALN-CC5
- Mean maximum C5 knockdown (relative to baseline) of 98.2 ± 0.3%; maximum up to 98.7%
- Minimum residual C5 levels of 0.9 mcg/mL

Complement Classical Pathway inhibition (CCP C5b-9 ELISA)
- Mean maximum CCP inhibition (relative to baseline) of 94.2 ± 1.7%; maximum up to 96.7%
- Similar results observed with alternative pathway assay (CAP C5b-9 ELISA)

Inhibition of sheep red blood cell (sRBC) hemolysis
- Mean maximum hemolysis inhibition (relative to baseline) of 75.6 ± 4.5%; maximum up to 81.5%
- Similar results to those observed in healthy volunteers

Serum C5

[Graphs showing C5 (mcg/mL) values over days since first visit]

CCP

[Graphs showing CCP activity (%) over days since first visit]

sRBC Hemolysis

[Graphs showing hemolysis (%) over days since first visit]

- 0081 - 200 mg ALN-CC5 x 13 q1W, then 400 mg x 4 q1W
- 0082 - 200 mg ALN-CC5 x 13 q1W, then 400 mg x 4 q1W
- 0061 - 400 mg ALN-CC5 x 8 q1W

*Based on data transferred up to 06June2016
**Initial ALN-CC5 Phase 1/2 Part C Study Results***

**Effects on LDH in Ecu Naïve Patients**

**During ALN-CC5 treatment, LDH levels were monitored**

- Maximum LDH reduction (relative to baseline) of 37% and 50% for Patients 0082 and 0081, respectively
  - However, LDH levels remained >1.5 x ULN
- LDH lowering not observed in Patient 0061 who had lower LDH at baseline and received only 8 ALN-CC5 doses

![Graph showing LDH levels over time for Patients 0081, 0082, and 0061.](image-url)

*Based on data transferred up to 06June2016*
Initial ALN-CC5 Phase 1/2 Part C Study Results*
Exploratory Data Analysis of Potential for Reducing Ecu

Standard treatment of PNH with Ecu requires high doses and frequent IV infusions
- Initial induction doses are 600 mg qW x4 followed by maintenance doses of 900 mg q2W

Effect of ALN-CC5-mediated C5 knockdown on LDH with reduced Ecu dose and frequency
- After ALN-CC5 dosing was completed, Ecu naïve patients were initiated on Ecu for residual hemolysis
- In the setting of ongoing ALN-CC5-mediated knockdown of serum C5 (>95%), investigators chose to administer a single dose of Ecu (600 mg) and monitor clinically
- All 3 patients achieved lowering of LDH <1.5x ULN which was sustained out to 4 weeks
- Provides exploratory evidence for potential to reduce Ecu dose and frequency of administration
  - To be confirmed and explored further in Phase 2 studies

<table>
<thead>
<tr>
<th>Patient</th>
<th>LDH (UI/L) Days post Ecu single dose (600mg)</th>
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<tbody>
<tr>
<td></td>
<td>Day 0</td>
</tr>
<tr>
<td>0061</td>
<td>426</td>
</tr>
<tr>
<td>0081</td>
<td>874</td>
</tr>
<tr>
<td>0082</td>
<td>1089</td>
</tr>
</tbody>
</table>

LDH ULN: 214-225 (1.5 X ULN values: 321-338)
ND – not determined; samples were not collected

*Based on data transferred up to 06June2016
Part C: Multiple Dose (MD): Patients with PNH

Open label, N = 6

Primary objectives:
- Safety, tolerability

Secondary objectives:
- PK, C5, LDH
- Complement activity assessment

ALN-CC5 dosed subcutaneously in 200 mg/mL solution
Initial ALN-CC5 Phase 1/2 Part C Study Results*
C5 KD and Complement Inhibition in Background Ecu Patients

Serum C5 KD following multiple doses of ALN-CC5
• Starting levels of total C5 markedly higher as compared with Ecu naïve patients
  ◦ Validated LC-MS assay measures total C5 – both bound and unbound to Ecu
  ◦ Suggests that Ecu treatment may lead to increased total C5 levels
• Mean maximum C5 knockdown (relative to baseline) of 86.7 ± 5.6%; maximum up to 97.8%
• Minimum residual C5 levels of 7.9 mcg/mL

Inhibition of complement activity:
• Residual complement activity as measured in CCP assay: <2% (from day 21 onward)
• Residual sheep red blood cell (sRBC) hemolysis: <3% (from day 21 onward)
• In two background Ecu patients (0063, 0064), normal LDH at baseline maintained during ALN-CC5 treatment

Breakthrough hemolysis in patient 0083 at Day 0 reflected in complement inhibition assays
Initial ALN-CC5 Phase 1/2 Part C Study Results*

Effects on LDH in Ecu Inadequate Responder Patient

In Ecu inadequate responder (Patient 0083), ALN-CC5 demonstrated preliminary evidence of clinical activity

- LDH of 966 IU/L at Day 0 while patient received Ecu at above labeled dose (1200 mg, q2W)
- LDH lowering to within reference range by Day 35 with ALN-CC5 treatment
  - Hemoglobin improved from 10.0 g/dL (Day 0) to up to 11.1 g/dL
  - Occurrence of viral gastroenteritis on Day 63 associated with transient breakthrough hemolysis
- Ecu reduced to labeled dose (900 mg, q2W) on Day 56
  - LDH control maintained out to Day 112

*Based on data transferred up to 06June2016. Sample collected at Day 140 was found hemolyzed; data not shown.
Initial ALN-CC5 Phase 1/2 Part C Study Results*

Increased Pre-Dose Ecu Levels with ALN-CC5 Treatment

Serum C5 KD with ALN-CC5 results in >3x increase in pre-dose Ecu trough levels

• Consistent with well-defined pharmacokinetics and target-mediated elimination of high-affinity antibodies

*Based on data transferred up to 06June2016

ALN-CC5 Phase 1/2 Study
Summary of Initial Part C Study Results*

**Summary**

- ALN-CC5 is a novel investigational approach for potential treatment of complement-mediated diseases, including PNH
- Part C includes Ecu naïve (N=3) and Background Ecu (N=3) patients with PNH
  - Includes one Ecu inadequate responder experiencing breakthrough hemolysis on 1200 mg Ecu q2W
- ALN-CC5 generally well tolerated with most AEs mild or moderate in severity
  - One severe AE possibly related to ALN-CC5 was reported as an asymptomatic, transient elevation of ALT and AST (grade 3) with no increase of total bilirubin
- In Ecu naïve patients, ALN-CC5 achieved robust C5 KD, inhibition of complement activity and modest lowering of LDH, but >1.5x ULN
- In Ecu naïve patients, preliminary evidence observed that supports a reduced Ecu dose and frequency
  - Following ALN-CC5, normalization of LDH achieved for 4 weeks with single 600 mg dose of Ecu
    - Represents 25% of Ecu induction labeled dose
- In background Ecu patients, ALN-CC5 achieved robust C5 KD and inhibition of complement activity
  - In Ecu inadequate responder patient, ALN-CC5 demonstrated preliminary evidence of clinical activity
    - Normalized LDH <1.5x ULN and improved hemoglobin levels
    - Ability to lower Ecu to label dose of 900 mg q2W
    - Achieved higher Ecu plasma concentration trough levels

*Based on data transferred up to 06June2016*
ALN-CC5 Phase 1/2 Study

Next steps

• Based on durability of ALN-CC5 effects, ongoing patient follow up with collection of PD, LDH, and Ecu PK data
  ◦ Ecu doses of 600 mg monthly are anticipated to maintain reductions in LDH in the setting of durable ALN-CC5 pharmacology

• Evaluate ALN-CC5 as part of potential new treatment paradigm in PNH for reducing Ecu dose and frequency and to potentially improve disease control in Ecu inadequate responders
  ◦ Phase 2 studies in PNH patients treated with ALN-CC5 dosed in combination with Ecu expected to start in 2016