



**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 11, 2016



# Agenda

## Welcome

- Christine Lindenboom  
Vice President, Investor Relations and Corporate Communications

## Introduction

- John Maraganore, Ph.D.  
Chief Executive Officer

## Review of Interim ALN-CC5 Phase 1/2 Data

- Pushkal Garg, M.D.  
Senior Vice President, Clinical Development

## Q&A Session

# Anylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of our drug candidates, obtain, maintain and protect intellectual property, enforce our patents and defend our patent portfolio, obtain regulatory approval for products, establish and maintain business alliances; our dependence on third parties for access to intellectual property; and the outcome of litigation, as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.



**John Maraganore, Ph.D.**  
**Chief Executive Officer**

# **Introduction**



**Pushkal Garg, M.D.**  
**Senior Vice President, Clinical Development**

# **Review of Interim ALN-CC5 Phase 1/2 Data**

# Paroxysmal Nocturnal Hemoglobinuria (PNH)

## Background

- Bone marrow defect due to acquired PIG-A gene mutation
  - Leads to deficiency of glycosylphosphatidylinositol (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%<sup>1</sup>
- Considerable proportion of PNH patients on Ecu experience breakthrough hemolysis<sup>2</sup>
- Wide inter-individual variation in pharmacodynamics and clearance of Ecu<sup>2-4</sup>
- Discrepancy between Ecu's labeled effective trough level of 35 mcg/mL (ref label) versus expert recommendations of at least 150 mcg/mL<sup>2</sup>
- QoL and economic burden associated with need for frequent Ecu IV infusions

## Unmet need for new complement inhibitors remains

<sup>1</sup> Int Archs Allergy Appl Immun; 48: 706-720 (1975), <sup>2</sup>de Latour RP, et al, Blood;125:775-83 (2015)

<sup>3</sup>Jodele S, et al. BBMT (2015), <sup>4</sup>Gatault P, et al, mAbs; 7:1205-11 (2015)

# 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

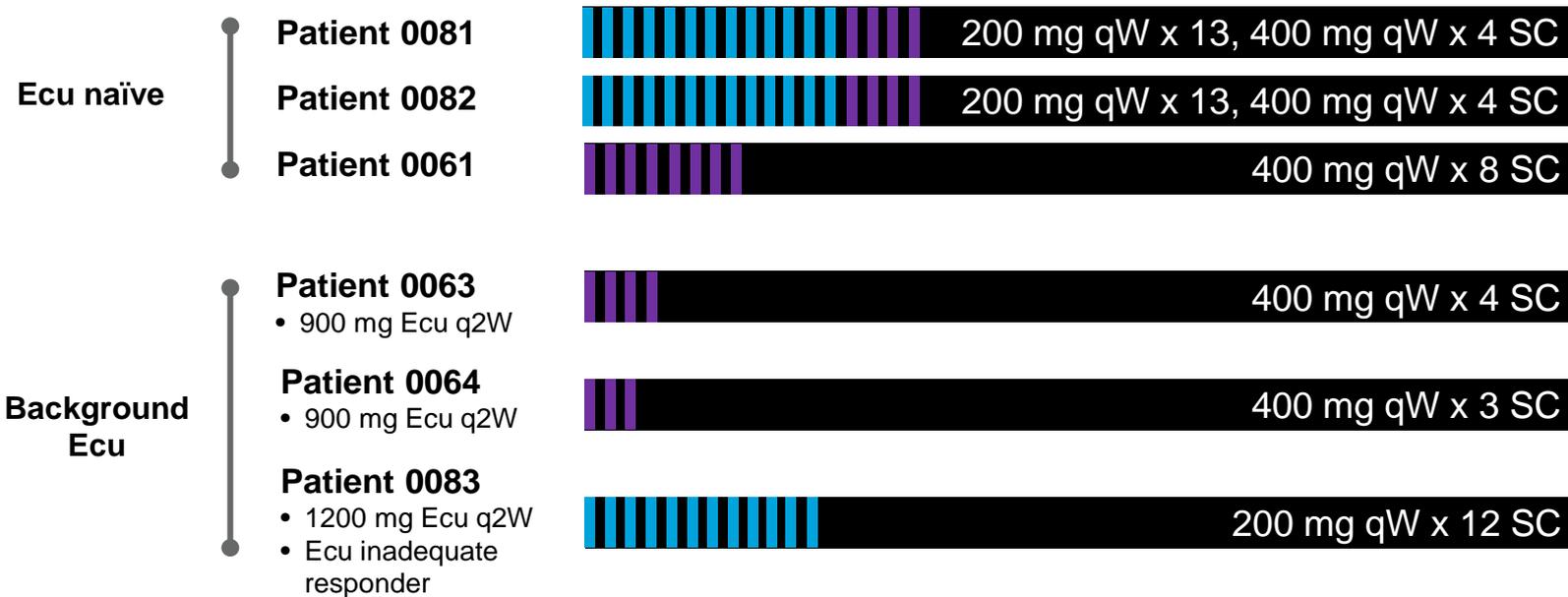
## In Part C of study, exploratory evaluation of ALN-CC5 and hepatic C5 knockdown for the treatment of PNH

- 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

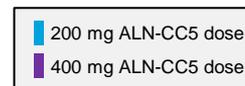


#### Primary objectives:

- 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\*

## 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  $\geq 2$  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)

# 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  $98.2 \pm 0.3\%$ ; 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  $94.2 \pm 1.7\%$ ; maximum up to 96.7%
- Similar results observed with alternative pathway assay (CAP C5b-9 ELISA)

### Inhibition of sheep red blood cell (sRBC) hemolysis

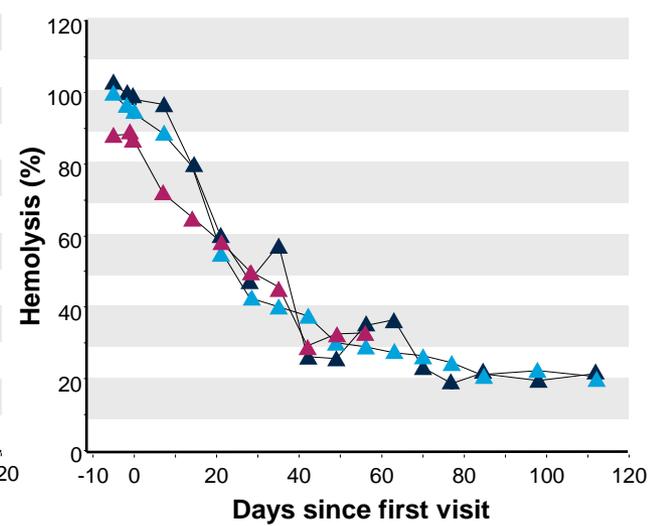
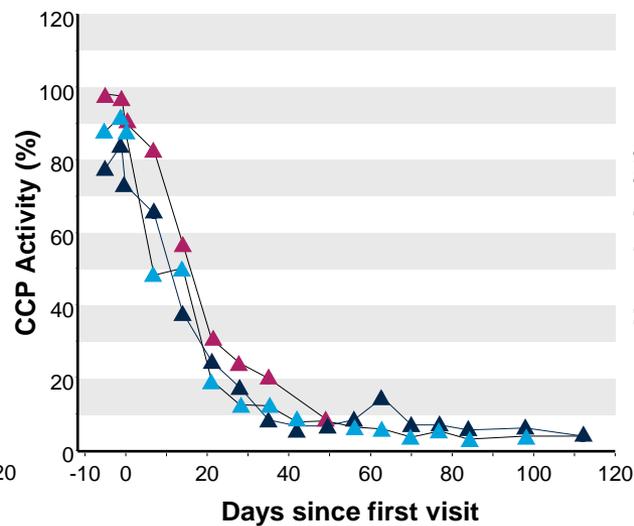
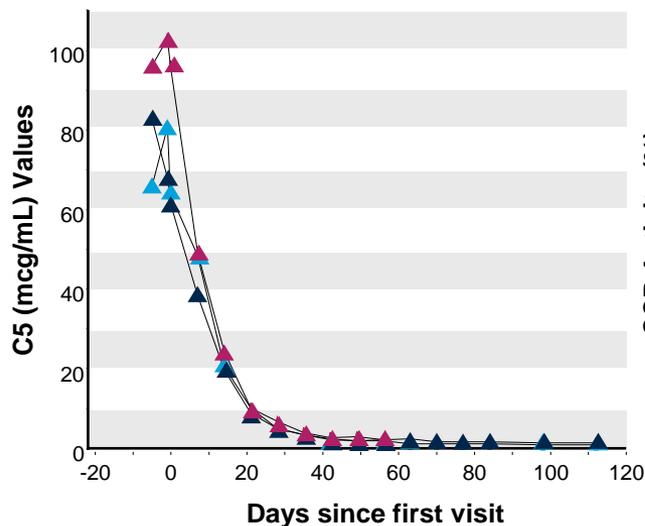
- Mean maximum hemolysis inhibition (relative to baseline) of  $75.6 \pm 4.5\%$ ; maximum up to 81.5%

Similar results to those observed in healthy volunteers

Serum C5

CCP

sRBC Hemolysis



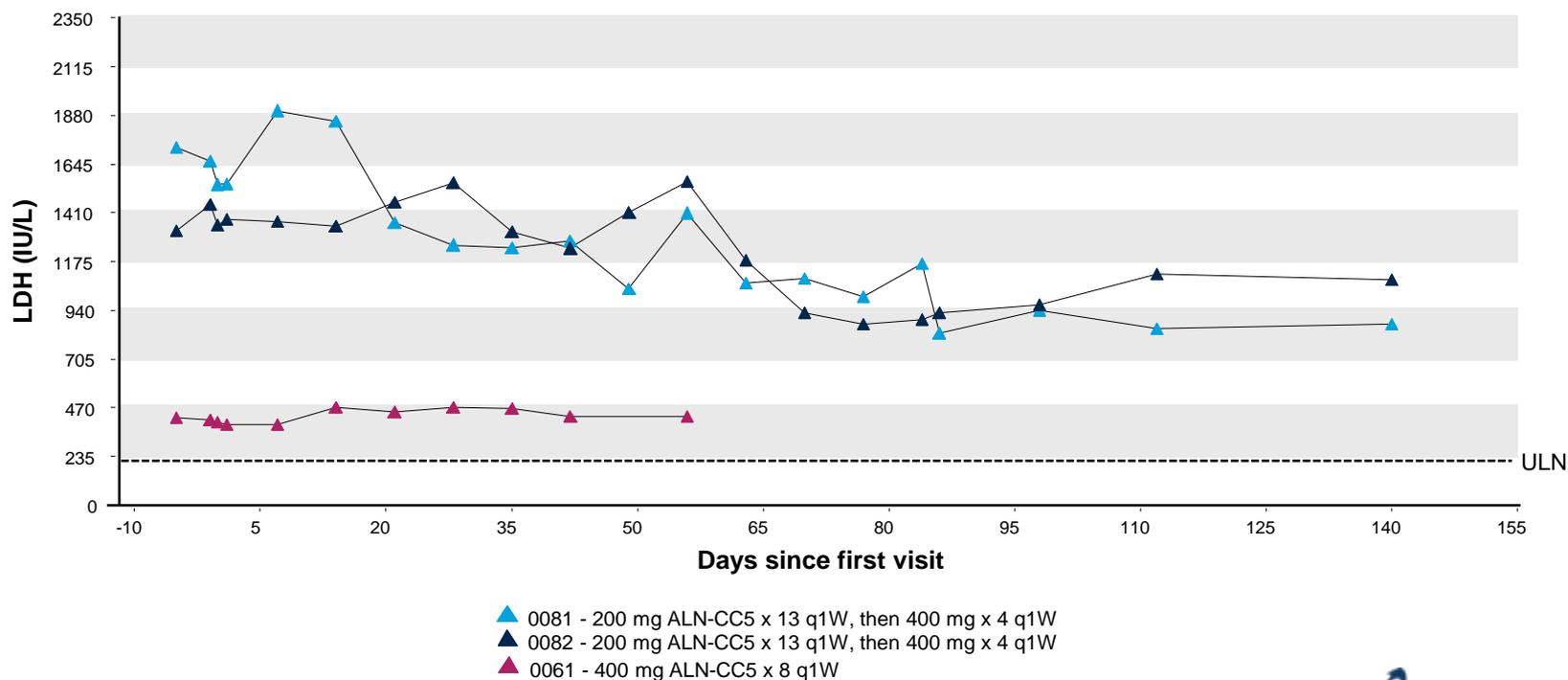
- ▲ 0081 - 200 mg ALN-CC5 x 13 q1W, then 400 mg x 4 q1W
- ▲ 0082 - 200 mg ALN-CC5 x 13 q1W, then 400 mg x 4 q1W
- ▲ 0061 - 400 mg ALN-CC5 x 8 q1W

# 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  $>1.5 \times$  ULN
- LDH lowering not observed in Patient 0061 who had lower LDH at baseline and received only 8 ALN-CC5 doses



# 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

Patient	LDH (UI/L)		
	Days post Ecu single dose (600mg)		
	Day 0	Day 14	Day 28
0061	426	217	222
0081	874	ND	224
0082	1089	ND	280

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

# Initial ALN-CC5 Phase 1/2 Part C Study Results\*

## C5 KD and Complement Inhibition in Background Ecu Patients

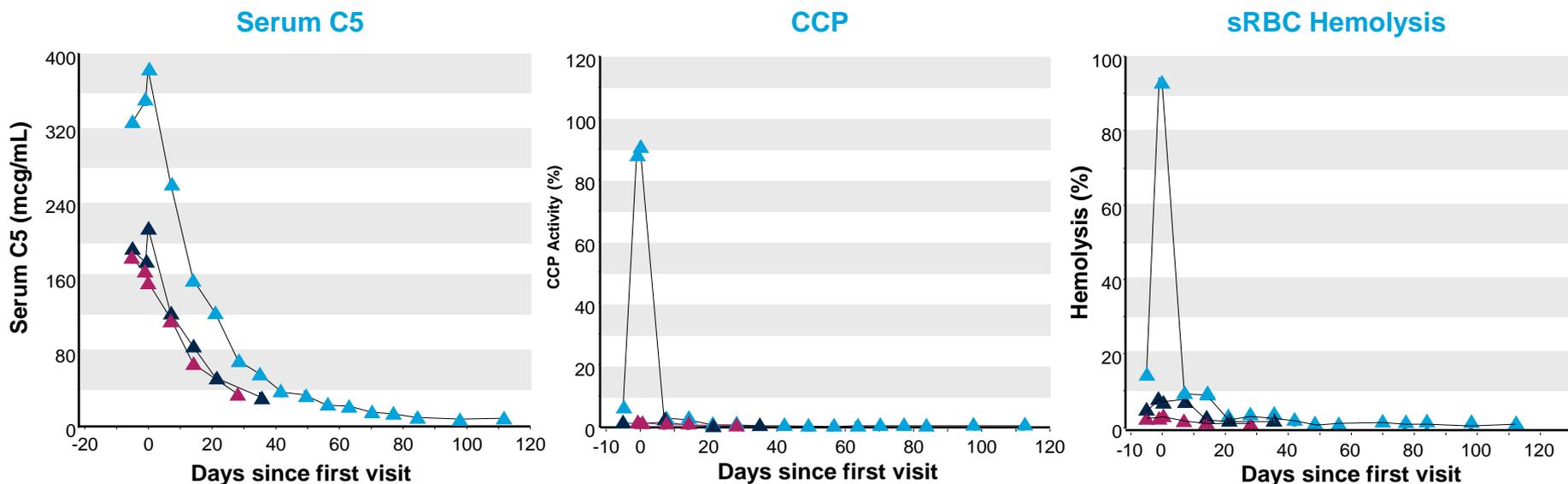
### Serum C5 KD following multiple doses of ALN-CC5

- 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  $86.7 \pm 5.6\%$ ; 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



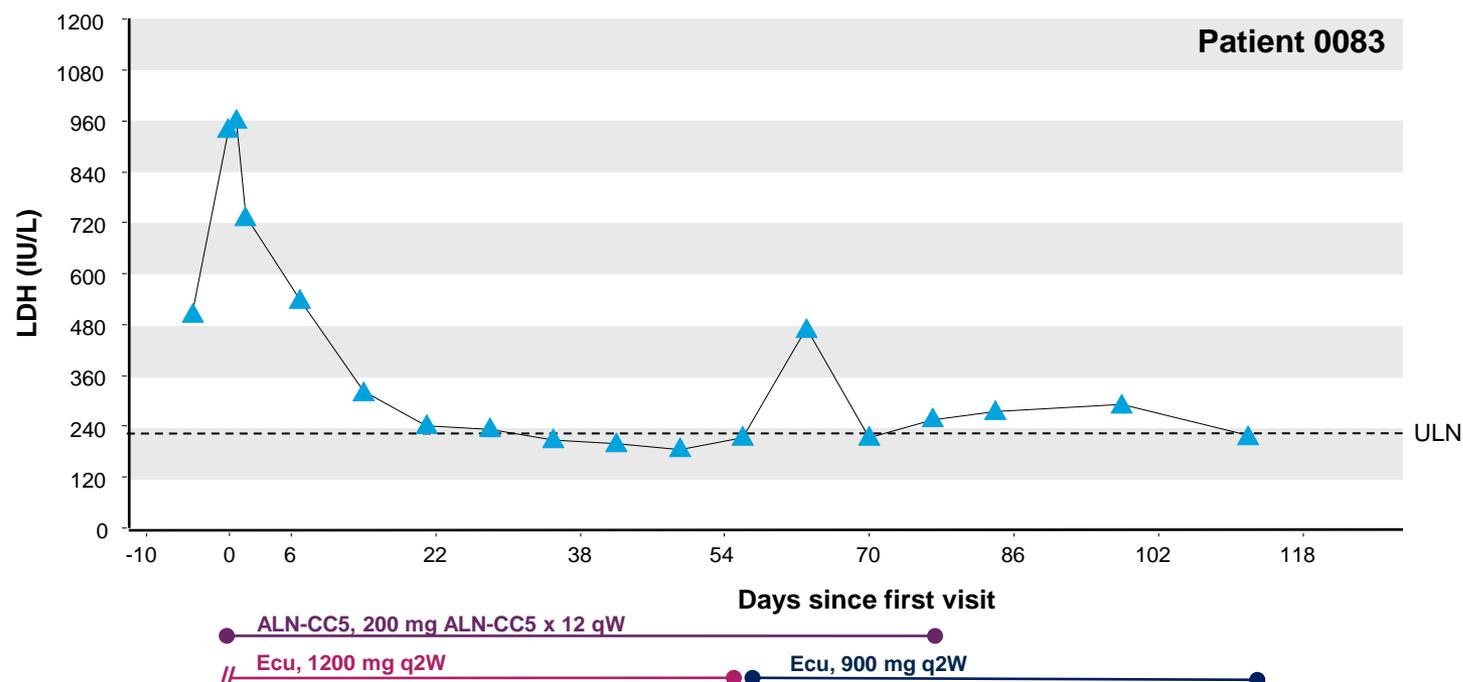
- ▲ 0083 - 200 mg ALN-CC5 x 12 q1W with 1200 mg Ecu x 4 q2W then 900 mg q2W
- ▲ 0063 - 400 mg ALN-CC5 x 4 q1W with 900 mg Ecu q2W
- ▲ 0064 - 400 mg ALN-CC5 x 3 q1W with 900 mg Ecu q2W

# 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

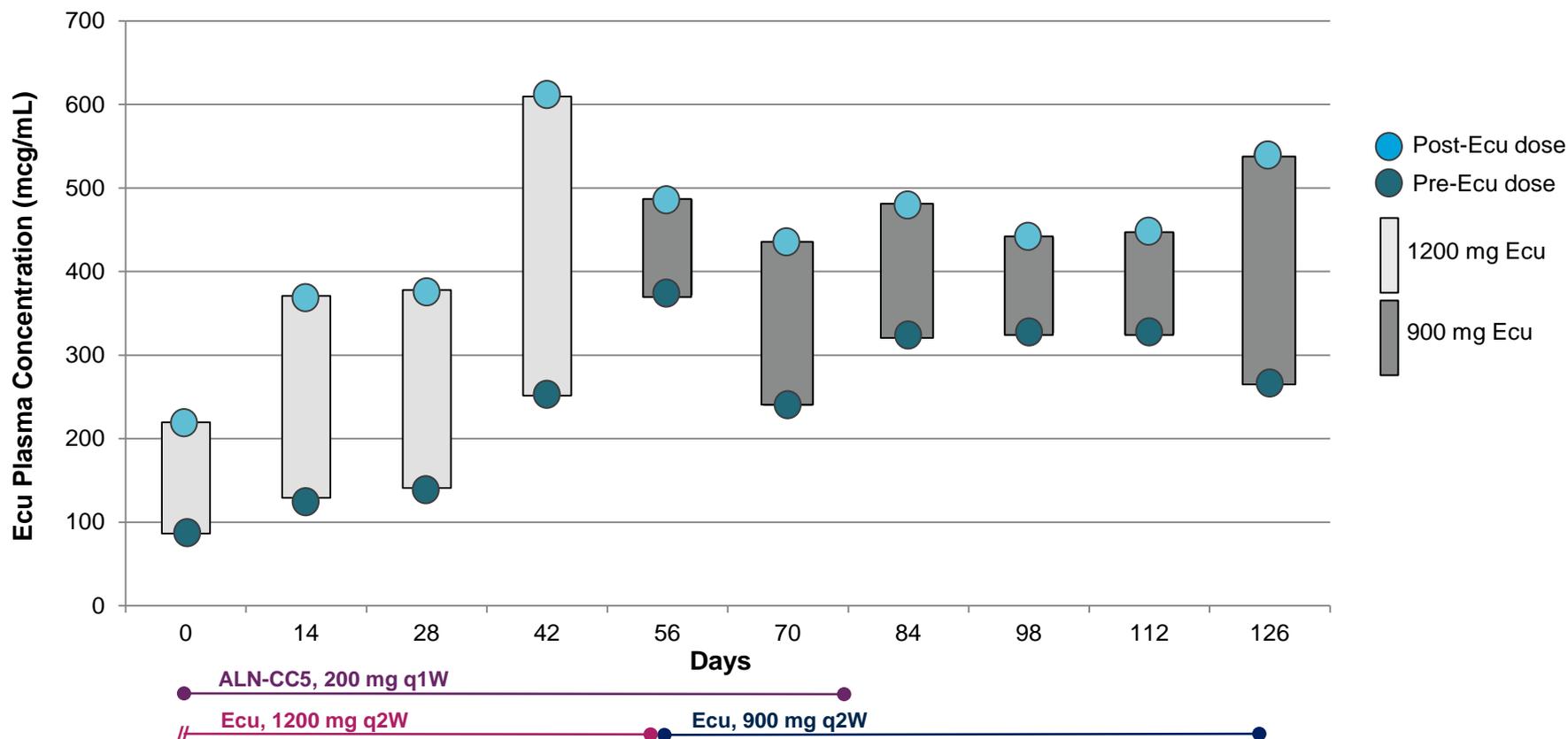


# Initial ALN-CC5 Phase 1/2 Part C Study Results\*

## 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<sup>1</sup>



\*Based on data transferred up to 06June2016

<sup>1</sup>Wang W et al. Clin Pharmacol & Ther; 84: 548-558 (2008)

# 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

# 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

# Q&A Session

**Thank You!**

