# 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

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# Paroxysmal Nocturnal Hemoglobinuria (PNH)

## Background

- Bone marrow defect due to acquired PIG-A gene mutation
  - Leads to deficiency of glycophosphatidylinositol (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

[1] Int Archs Allergy Appl Immun; 48: 706-720 (1975), [2]de Latour RP, et al, Blood;125:775-83 (2015)
[3]Jodele S, et al. BBMT (2015), [4]Gatault P, et al, mAbs; 7:1205-11 (2015)



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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

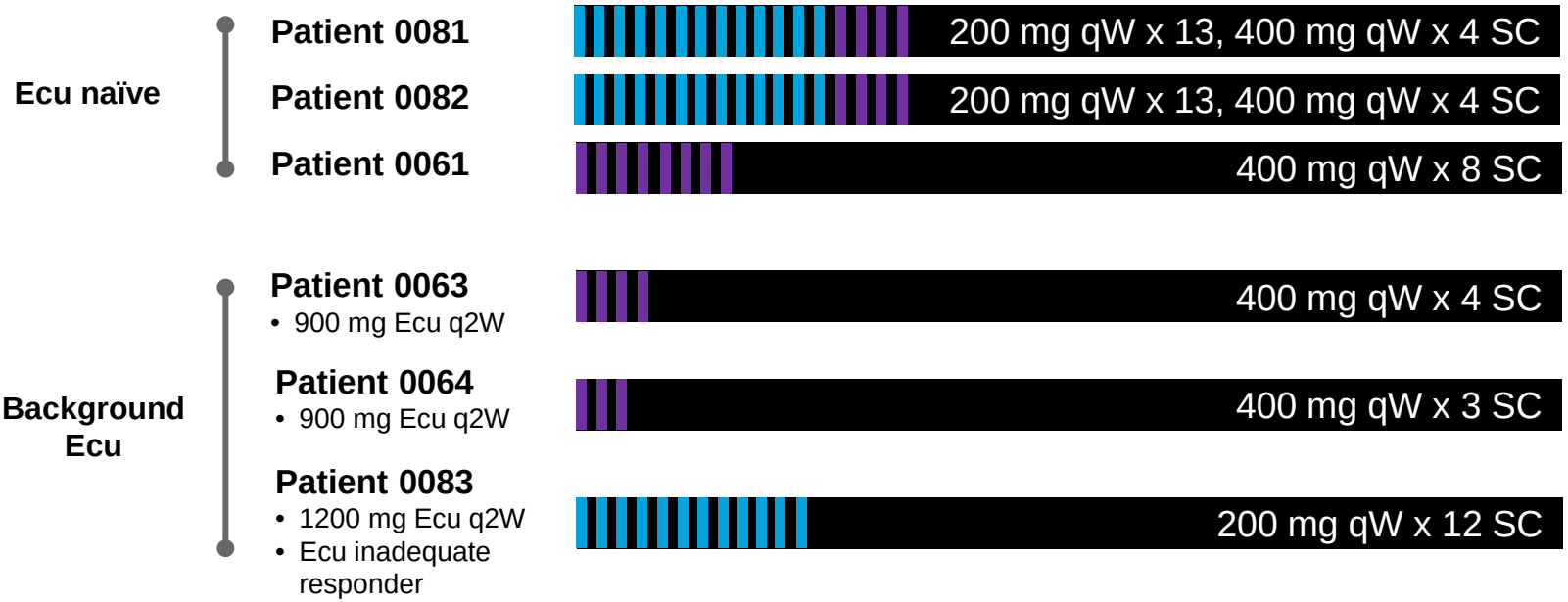
## In Part C of study, exploratory evaluation of ALN-CC5 and hepatic C5 knockdown for the treatment of PNH

- 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**




**Primary objectives:**

- Safety, tolerability

**Secondary objectives:**

- PK, C5, LDH
- Complement activity assessment

200 mg ALN-CC5 dose
400 mg ALN-CC5 dose

*ALN-CC5 dosed subcutaneously in 200 mg/mL solution*



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

## Demographics and Baseline Characteristics

### 6 Patients with PNH administered ALN-CC5

| Part C : PNH Patients | |
|---|---|
| Age (years), Mean (Min, Max) | 43.7<br>(25, 58) |
| Gender: Male(%) | 50% |
| BMI (kg/m$^2$), Mean | 24.6 |
| Race (%)<br>- Asian<br>- Black/African<br>- Caucasian<br>- Other | <br>0%<br>0%<br>100%<br>0% |
| Time on study, Mean (days) | 81 |



*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)



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# ALN-CC5 Phase 1/2 Study- Part C

## Patients with PNH – Ecu Naïve and on Background Ecu

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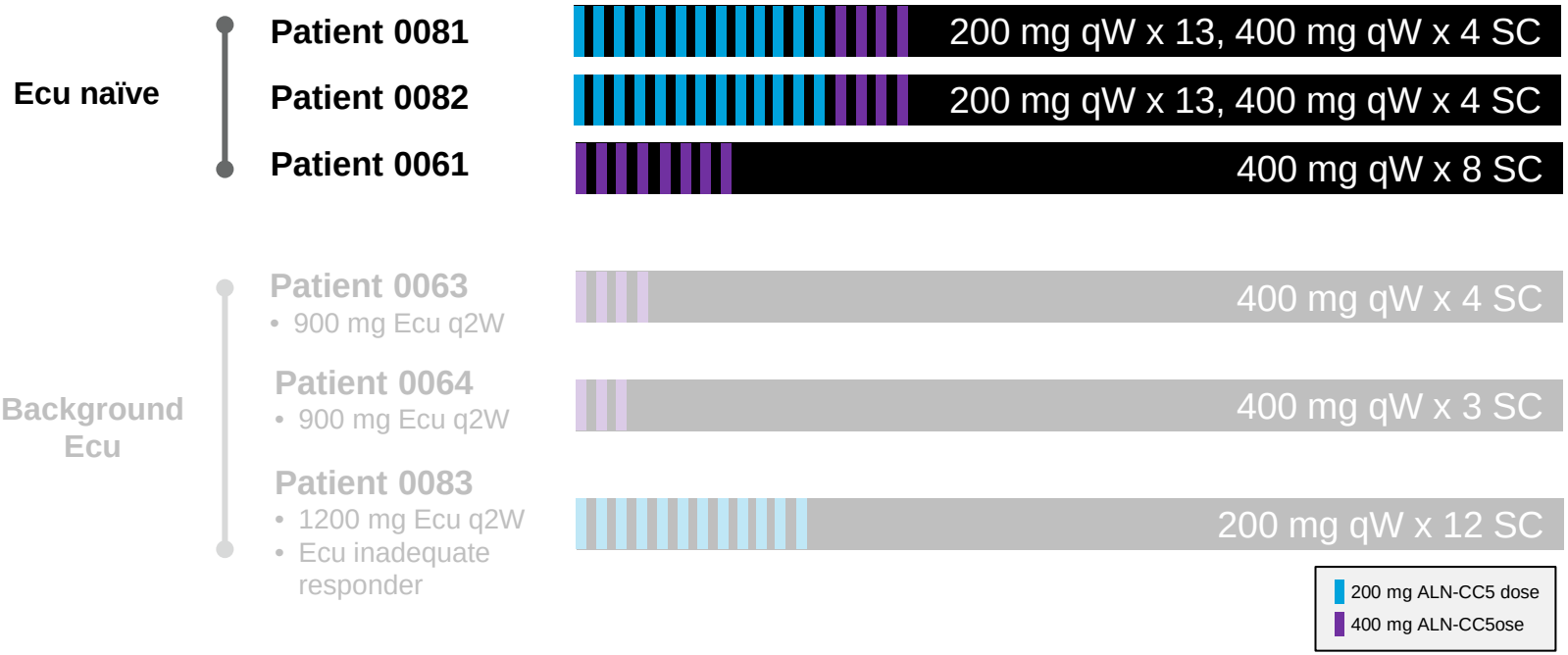


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*ALN-CC5 dosed subcutaneously in 200 mg/mL solution*

# 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

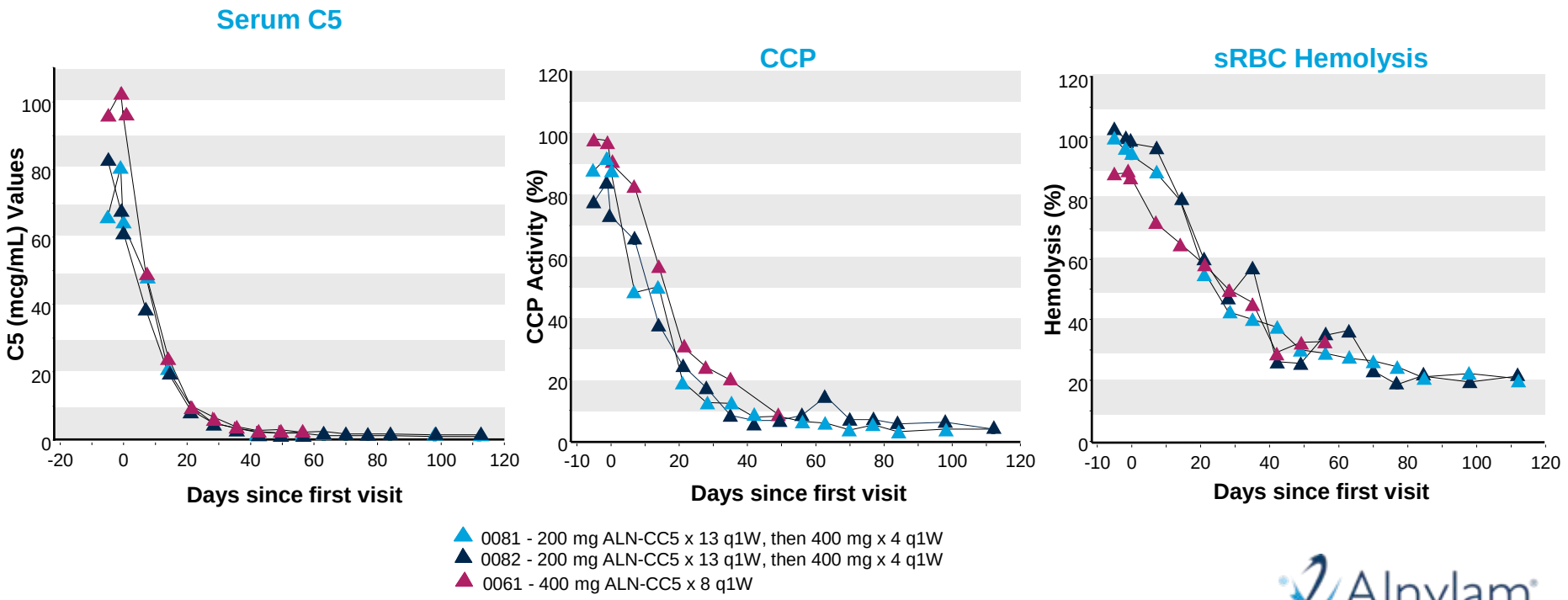
**Complement Classical Pathway inhibition (CCP C5b-9 ELISA)**

- 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**



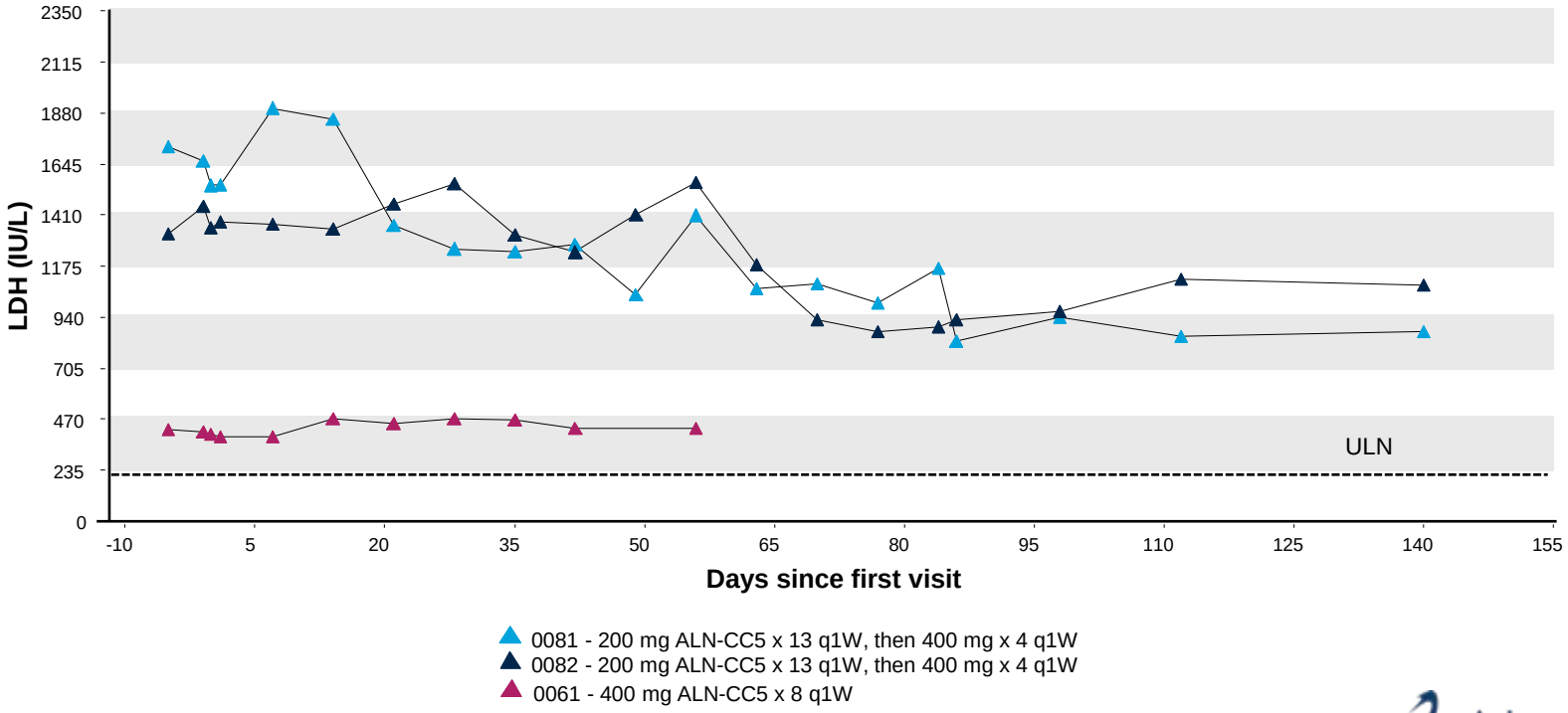

*Based on data transferred up to 06June2016

# 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






*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

| 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

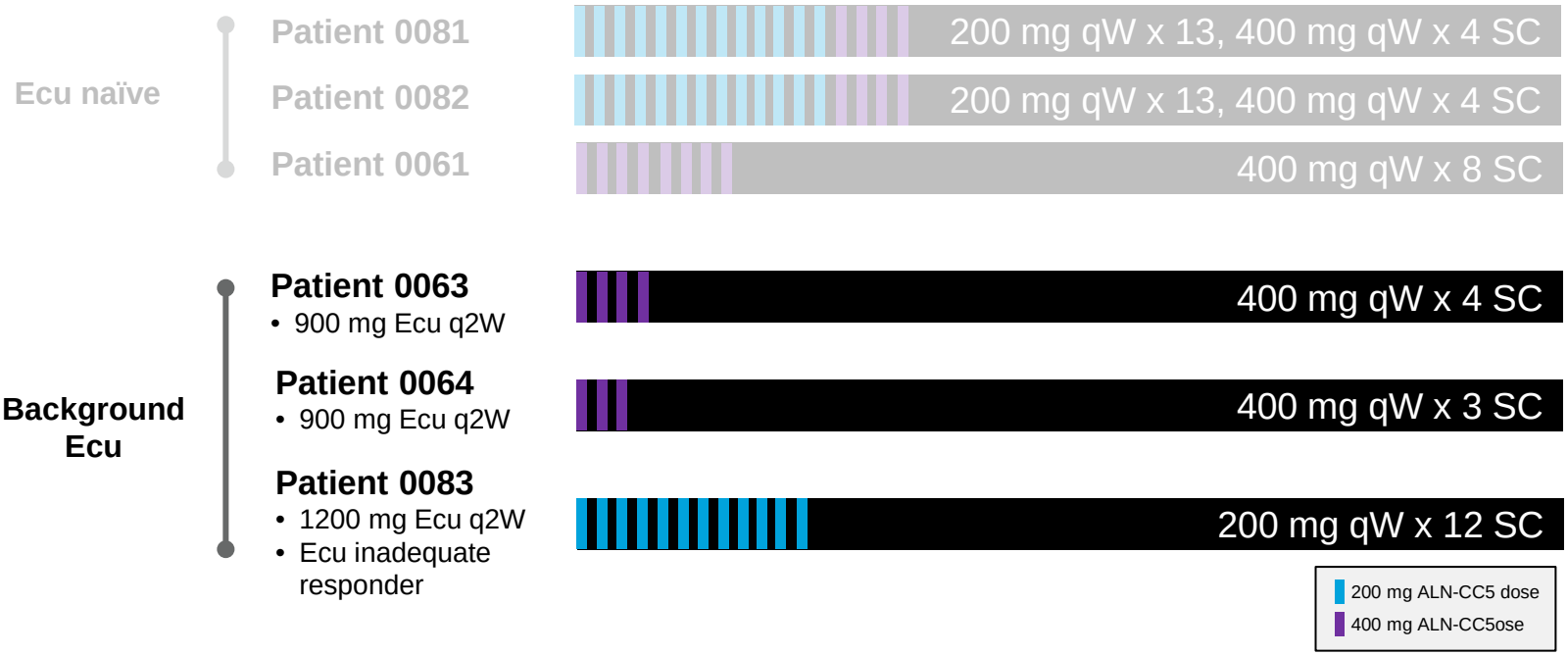


*Based on data transferred up to 06June2016

# 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**

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*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

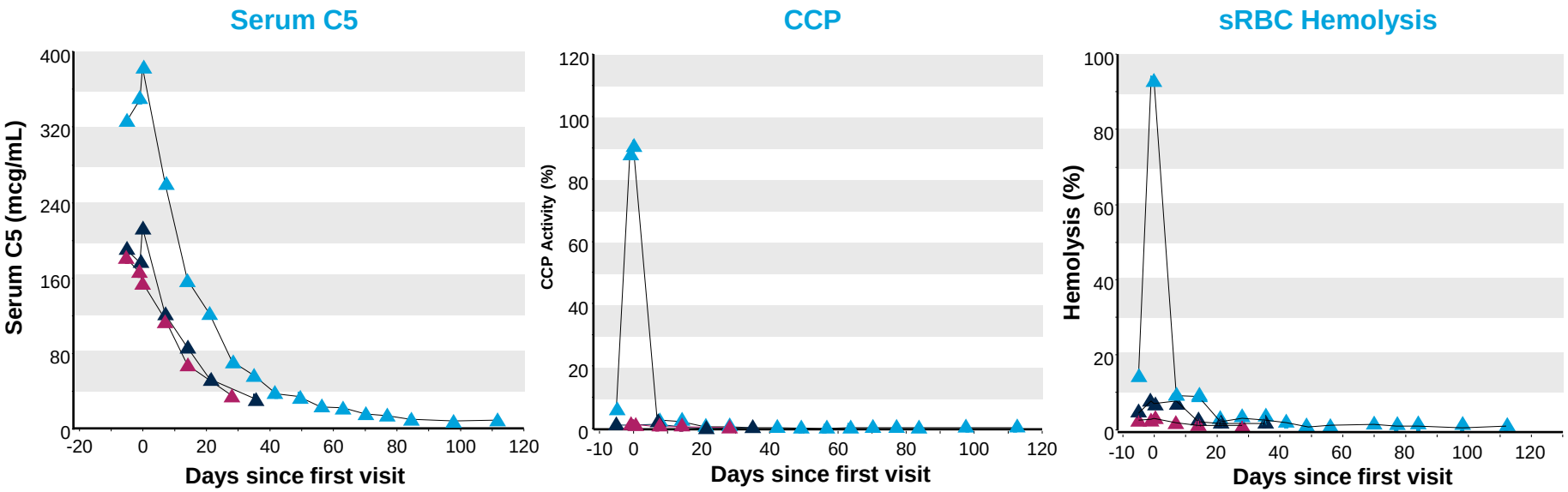
### Serum C5 KD following multiple doses of ALN-CC5

- 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




▲ 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



*Based on data transferred up to 06June2016

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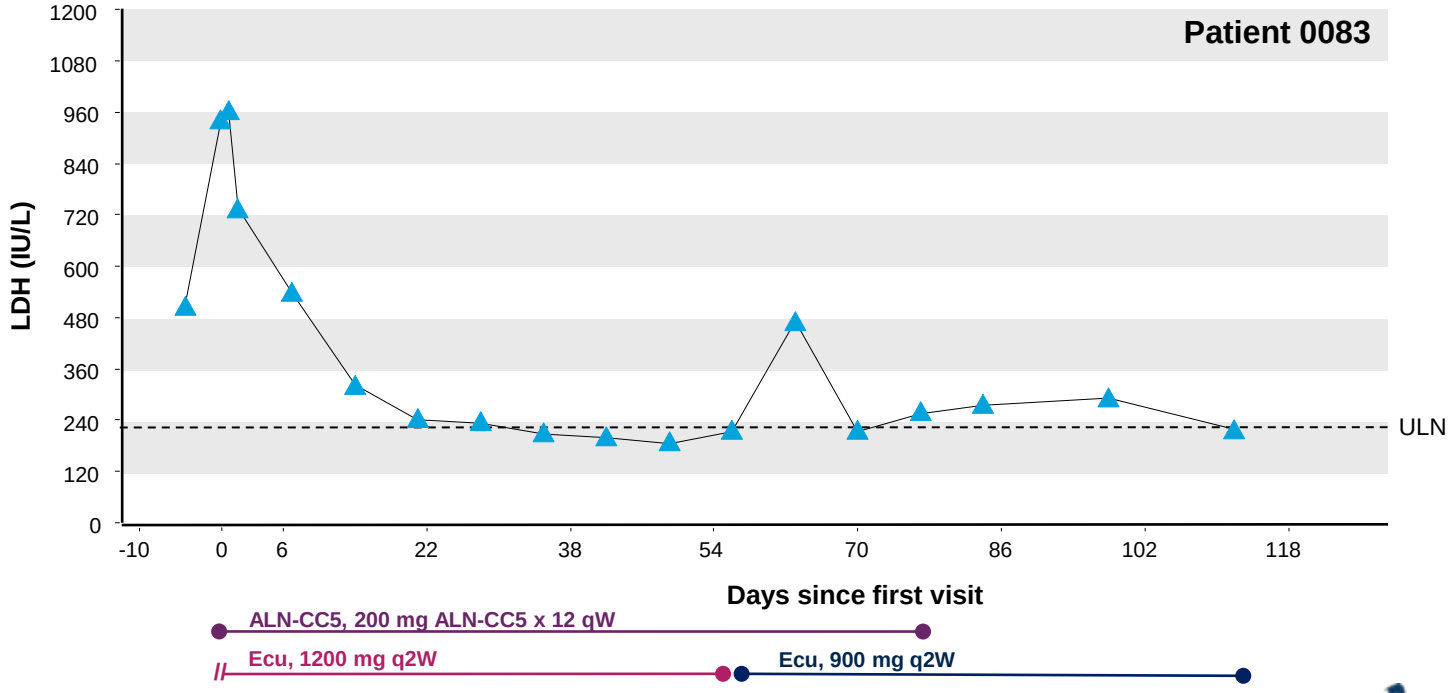
# Initial ALN-CC5 Phase 1/2 Part C Study Results*

## 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



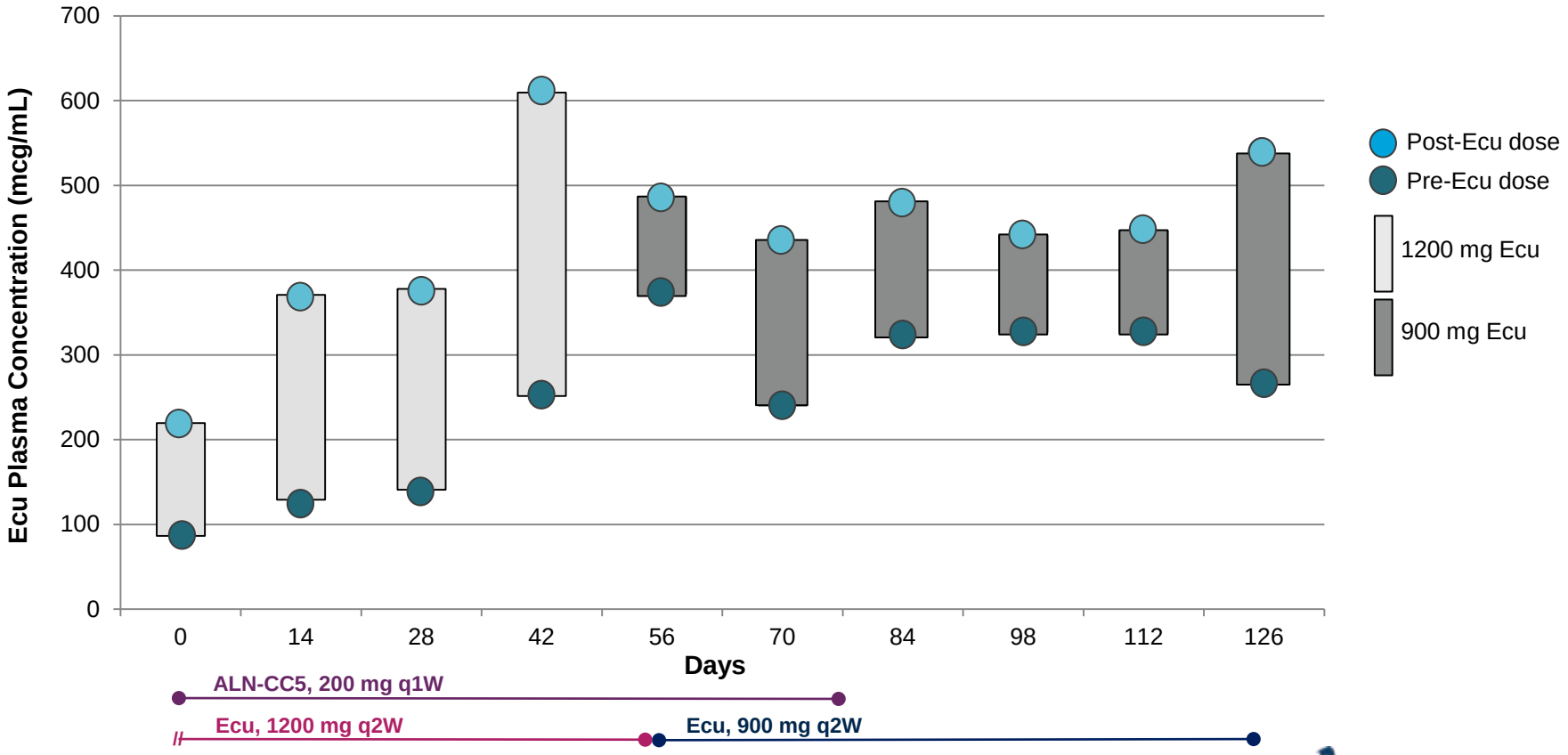

*Based on data transferred up to 06June2016. Sample collected at Day 140 was found hemolyzed; data not shown.

# 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[1]




*Based on data transferred up to 06June2016

[1]Wang W et al. Clin Pharmacol & Ther; 84: 548-558 (2008)



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# 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