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

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5 December 2016 | ASH | San Diego, CA

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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 (e.g., CD59) 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]
- QoL and economic burden associated with need for frequent Ecu IV infusions

Unmet need for new complement inhibitor 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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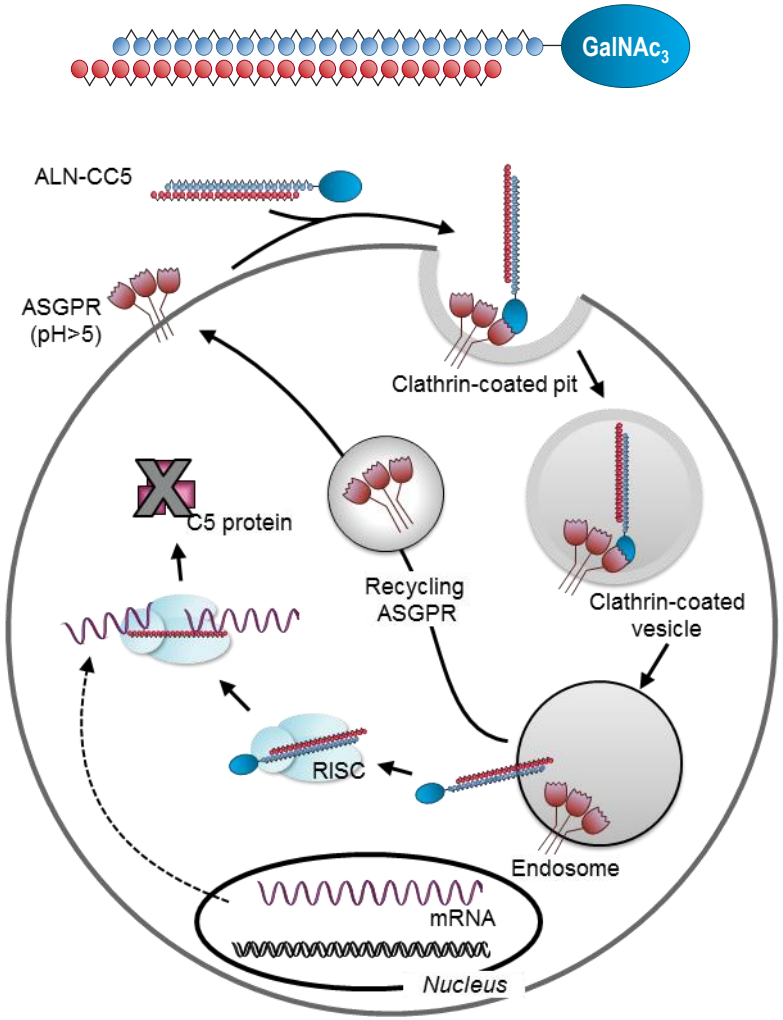
ALN-CC5

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 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 6 months after single dose



ClinicalTrials.gov Identifier: NCT02352493

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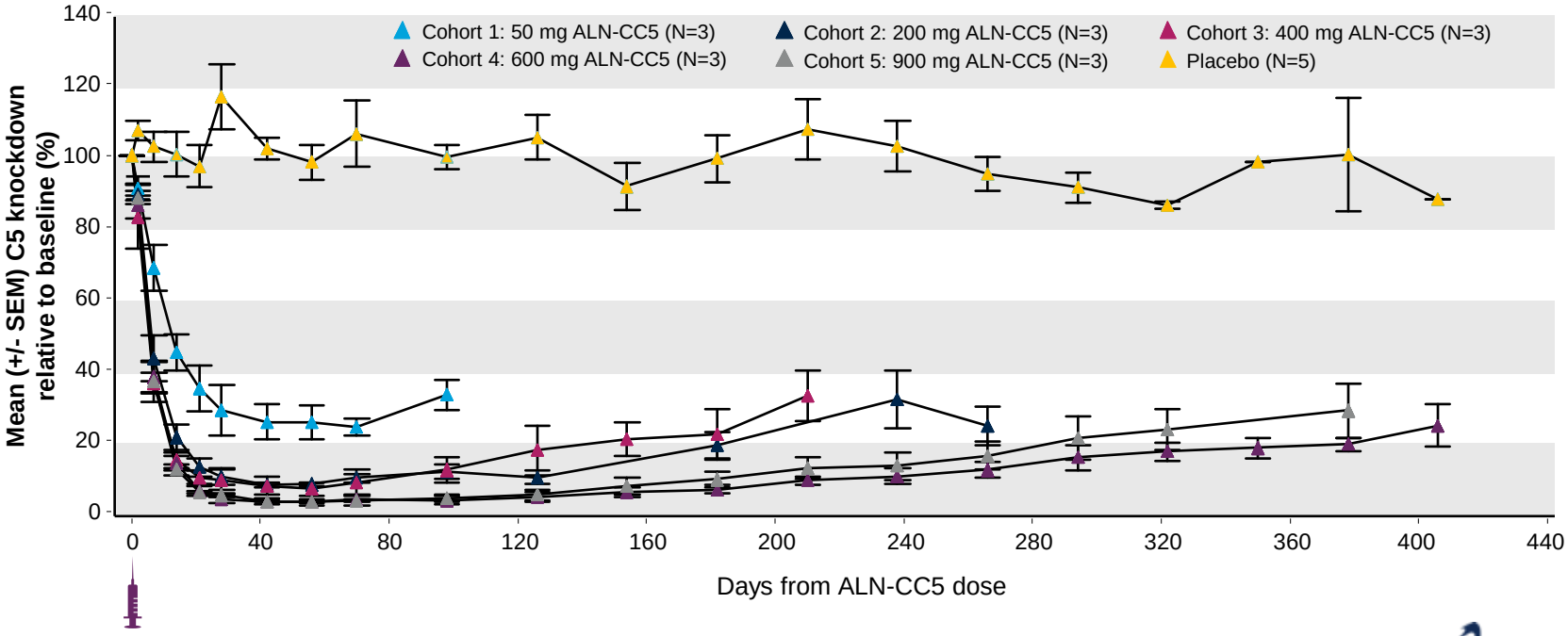
Interim ALN-CC5 Phase 1/2 (Part A, SAD) Study Results*

Pharmacodynamics and Clinical Activity: Serum C5

Updated 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% (600mg)
- Mean (± SEM) C5 knockdown:
  - Day 98 (600 mg): 97 ± 1.1%
  - Day 182 (600 mg): 94 ± 1.2%
  - Day 406 (600 mg): 76 ± 6.0%



SAD: Single ascending dose
*Data as of 13 October 2016

ALN-CC5 Phase 1/2 (Part C) Follow-up Rationale

Upon completion of ALN-CC5 dosing, investigator initiation of Ecu in setting of ongoing ALN-CC5 pharmacology permitted exploratory analysis of potential for reducing dose and frequency of Ecu

- Ecu naïve patients (N=3):
  - ALN-CC5 monotherapy achieved robust C5 KD, inhibition of complement activity and modest lowering of LDH, but >1.5 x ULN[1]
  - Subsequently, investigators initiated treatment with Ecu for residual hemolysis
- Background Ecu patients (N=3):
  - Included one subject with inadequate response to ecu, who was being treated with above-labeled doses of 1200 mg q2weeks
  - Plan to switch from Ecu to ALN-CC5 monotherapy discontinued due to results in Ecu-naïve patients (above)
  - Instead, investigators reduced Ecu frequency in setting of ongoing ALN-CC5 pharmacology

[1]Hill A, et al. Haematologica; 101(s1): 172 abstract n. S474 (2016)

Interim ALN-CC5 Phase 1/2 (Part C) Study Results*

Demographics and Baseline Characteristics

Part C : PNH Patients (n=6)	
Age, years; Mean (min, max)	43.7 (25, 58)
Gender, %; Male	50
BMI, kg/m^2; Mean	24.6
Race – Caucasian, %	100
Total time on study, days; Mean	256
Time in exploratory Ecu sparing, days; Mean	148

*Data as of 13 October 2016

Interim ALN-CC5 Phase 1/2 (Part C) Study Results*

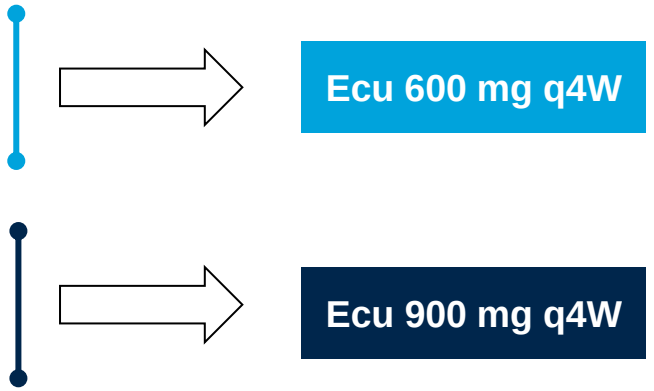
Exploration of Potential for Reducing Ecu Dose and Frequency

Part C ALN-CC5 dosing

Patient	Ecu Naïve or background Ecu	# of ALN-CC5 doses (200-400 qW)	C5 KD (%)†
0081	Ecu Naïve	17	98.4
0082	Ecu Naïve	17	98.0
0061	Ecu Naïve	8	97.8
0083	Background Ecu	12	97.5
0063	Background Ecu	4	92.8
0064	Background Ecu	3	97.1

†*C5 Knockdown at start of Ecu sparing*

Exploratory Ecu sparing



Dose and frequency of Ecu lowered after ALN-CC5 dosing completed

- Ecu naïve patients were started on 600 mg Ecu q4W
- Patients on background Ecu therapy were transitioned to spared regimen of 900 mg Ecu q4W

Patients followed every 2 weeks until study Day 280

- Monitoring of safety and laboratory parameters including LDH, PD and Ecu PK

*Data as of 13 October 2016
†C5 knockdown prior to the initiation of Ecu sparing

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Interim ALN-CC5 Phase 1/2 (Part C) Study Results*
Updated Safety and Tolerability Summary

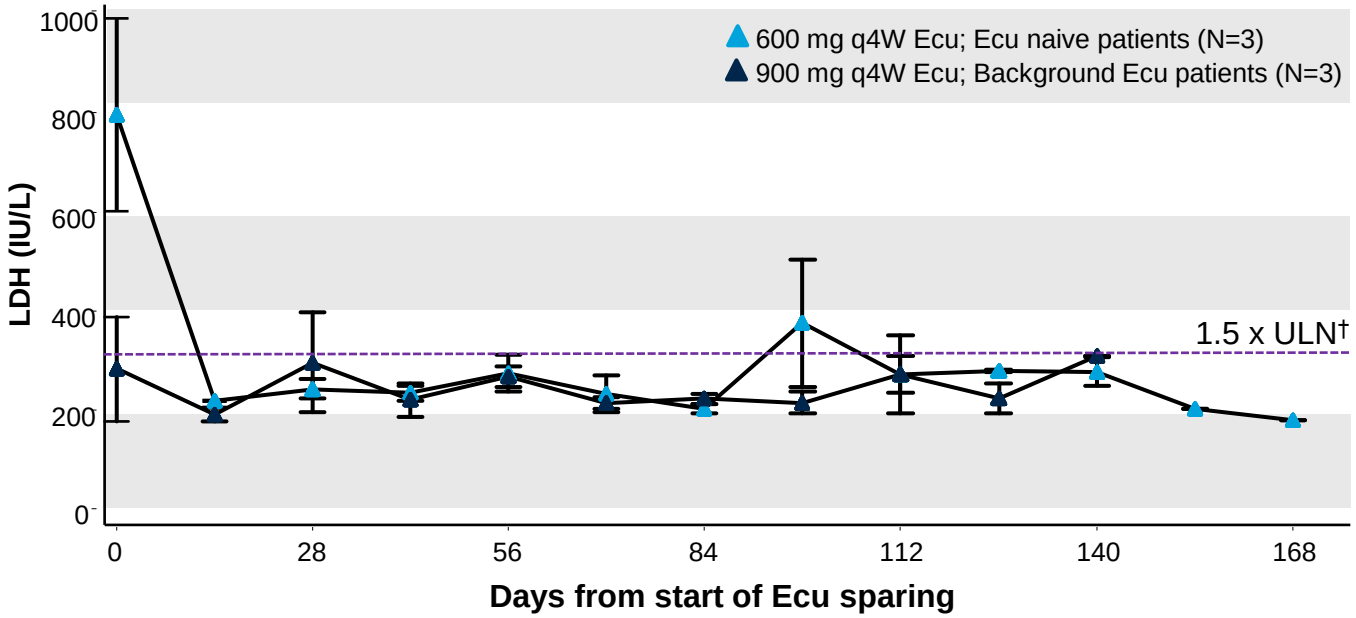
ALN-CC5 generally well tolerated in patients with PNH after multiple doses

- No SAEs or discontinuations due to AEs
- All 6 patients reported at least one AE
  - Majority of AEs mild to moderate in severity
  - 1 AE reported as hemolysis in setting of upper respiratory tract infection; moderate in severity and considered unrelated to study drug
  - 1 possibly related reported severe AE reported as hepatotoxicity (previously reported[1])
    - Asymptomatic, transient grade 3 elevation of ALT and AST without increase in total bilirubin
    - Under ongoing ALN-CC5 PD effects, liver enzyme levels returned to baseline on D182 until end of study (D280)
  - AEs reported in ≥ 2 patients: Fatigue, oropharyngeal pain (N=2 each)
  - 1 additional patient reported at least one possibly or definitely related AE
    - All AEs were mild injection site reactions (ISRs)
      - » Discomfort ; erythema and pain (N=1)
- No other clinically significant changes in vital signs, EKG, physical exams or clinical laboratories (hematology, biochemistry, coagulation and urinalysis)

*Data as of 13 October 2016
SAE, serious adverse event; AE, adverse event
[1]Hill A, et al. Haematologica; 101(s1): 172 abstract n. S474 (2016)

Interim ALN-CC5 Phase 1/2 (Part C) Study Results*

Effective Control of Intravascular Hemolysis with Spared Ecu



During ALN-CC5-mediated knockdown of serum C5, investigators administered Ecu at a spared dose and frequency and monitored patients clinically

- Ecu naïve patients: LDH < 1.5 x ULN achieved and maintained with 600 mg Ecu q4W‡
- Background Ecu patients: LDH < 1.5 x ULN maintained with 900 mg Ecu q4W
  - In patient with prior inadequate Ecu response, LDH normalization generally maintained with 900 mg q4W
- Dosing every 4 weeks (q4W) of 600 or 900 mg Ecu represents 33% or 50% of maintenance dose, respectively

*Data as of 13 October 2016

†*1.5x ULN values for LDH: 321-338 IU/L*

‡Patient 0081 experienced hemolysis on D98 due to viral URI, received 600 mg Ecu on D102 and q4W dosing resumed on D112

Interim ALN-CC5 Phase 1/2 (Part C) Study Results*

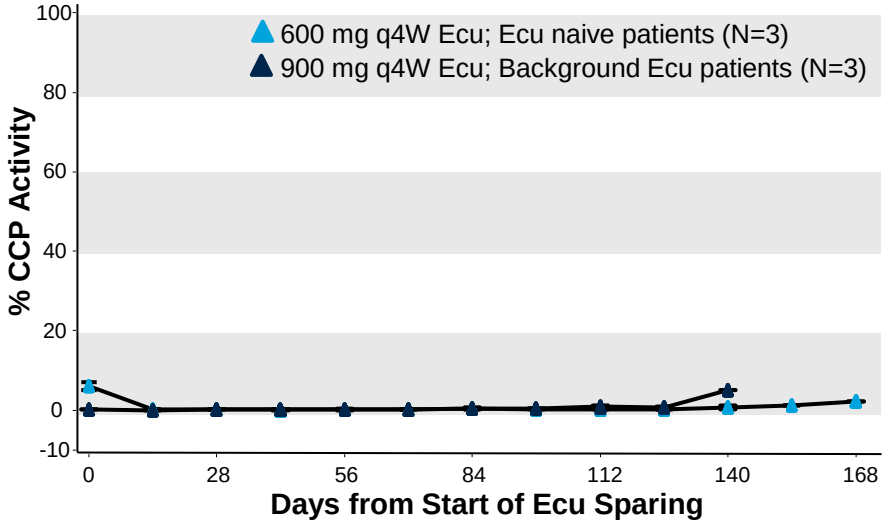
Exploratory Data of Potential for Reducing Ecu: Complement Inhibition

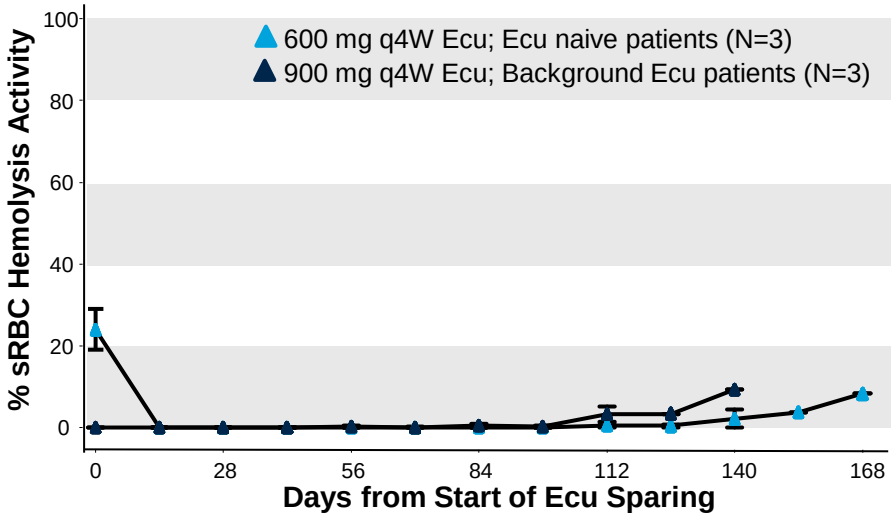
Complement activity inhibition

- CCP C5b-9 ELISA
  - CCP level at D84 since start of Ecu sparing: 0.3 ± 0.3% for 600 mg q4W, 0.4 ± 0.2% for 900 mg q4W
  - Similar results observed with alternative pathway assay (CAP C5b-9 ELISA)
- Sheep red blood cell (sRBC) hemolysis
  - sRBC level at day 84 since start of Ecu sparing: 0% for 600 mg q4W and 0.4 ± 0.4% for 900 mg q4W

Greater degree of complement inhibition observed with combination vs either Ecu or ALN-CC5 alone

- CCP levels in standard-of-care Ecu patients: 1.2 ± 0.1%; sRBC levels in standard of care Ecu patients: 4.5 ± 1.8%



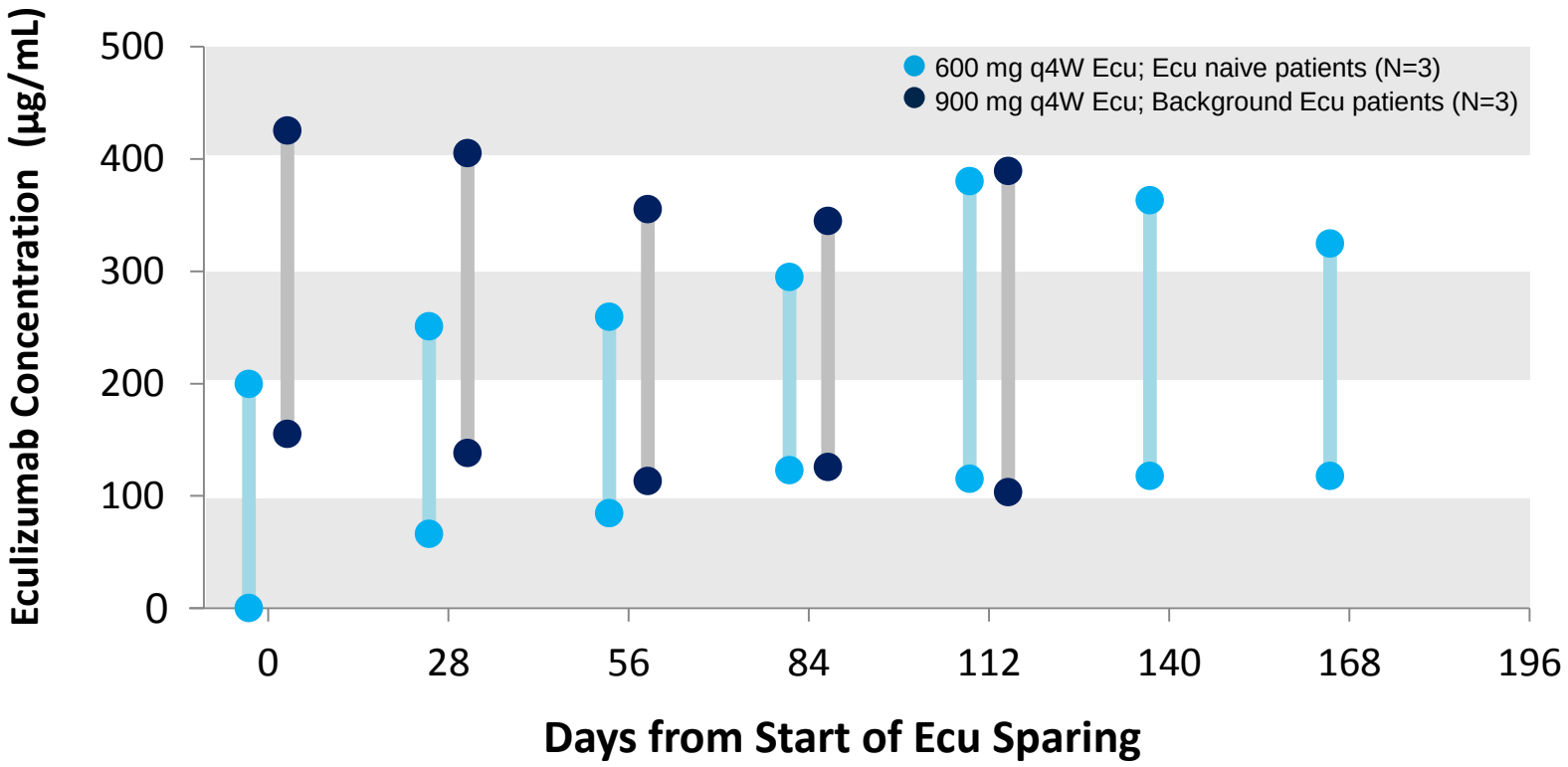


*Data as of 13 October 2016

Interim ALN-CC5 Phase 1/2 (Part C) Study Results*

Peak and Trough Ecu Levels with Spared Ecu Regimen

Trough levels sustained with monthly dosing of 600 mg or 900 mg



*Data as of 13 October 2016

Interim ALN-CC5 Phase 1/2 (Part C) Study Results*
Summary

ALN-CC5 is a novel investigational approach for treatment of complement-mediated diseases, including PNH

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 (D77)
  - Liver enzyme levels return to baseline on D182 under ongoing PD effects until end of study (D280)

In Ecu naïve and background Ecu patients during ongoing ALN-CC5 pharmacology, continued evidence supporting potential for reduced Ecu dose and frequency

- In Ecu naïve patients, normalization of LDH achieved for up to 6 months with 600 mg Ecu q4W
  - Represents 67% reduction of Ecu labeled maintenance dose
- In background Ecu patients, maintenance of LDH achieved for 5 months with 900 mg Ecu q4W
  - Represents 50% reduction of Ecu labeled maintenance dose
  - In background Ecu patient with prior inadequate response at 1200 mg q2W, LDH normalization was generally maintained with 900 mg q4W

*Data as of 13 October 2016

ALN-CC5 Phase 1/2 Study

Next steps

- Continue to 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

*Data as of 13 October 2016

Acknowledgements

Thank you to the patients, investigators, and study staff who participated in this study.

Country	PI Name	Location
United Kingdom	Anita Hill	Department of Haematology, Leeds Teaching Hospitals, Leeds, UK
	Jorg Taubel	Richmond Pharmacology Ltd, Tooting, UK
	Jim Bush	Covance Clinical Research Unit Limited, Leeds, UK
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