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

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ALN-CC5 and Complement-Mediated Diseases

Excessive complement activity drives disease pathophysiology in many indications

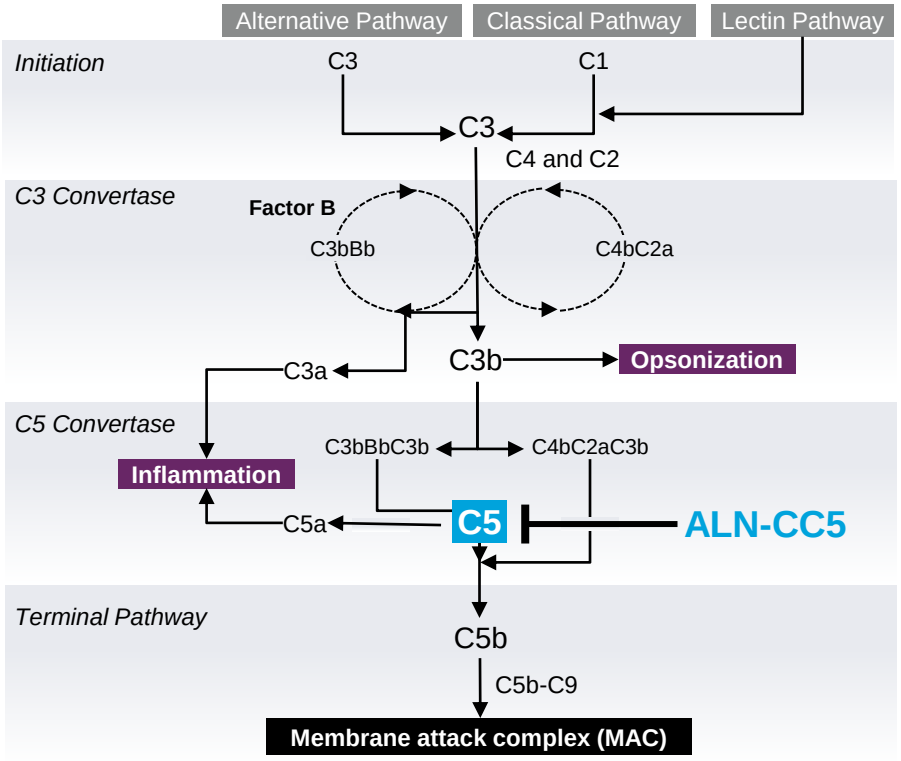
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Atypical hemolytic uremic syndrome (aHUS)
- Neuromyelitis optica (NMO)
- Myasthenia gravis (MG)
- Many others

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 PNH[1]

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 aHUS[1]

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

Current PNH Treatment Challenges

Poor Responders, Breakthrough Hemolysis & C5 Fluctuations

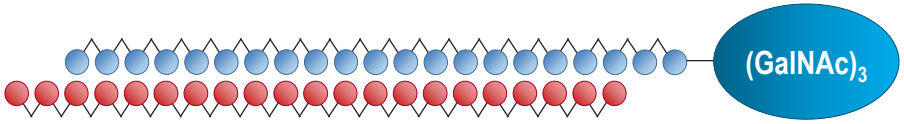
- Eculizumab is potent inhibitor of C5, however significant proportion of PNH patients experience breakthrough or occult hemolysis[1]
- Complement C5 is an acute phase protein and inflammation causes C5 fluctuations of up to ~100%[2]
- Wide inter-individual variation in pharmacodynamics and clearance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

[1]de Latour R, Blood 125(5):775-83 (2015); [2]Data illustration adapted from Int Archs Allergy appl Immun 48: 706-720 (1975), [3]Jodele S, et al. BBMT (2015); [4]Gatault P, et al, mAbs; 7:1205-11 (2015); [5]Haematologica 99(5): 922-929, (2014); [6]Korean Med Sci 31:214-221, (2016)

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

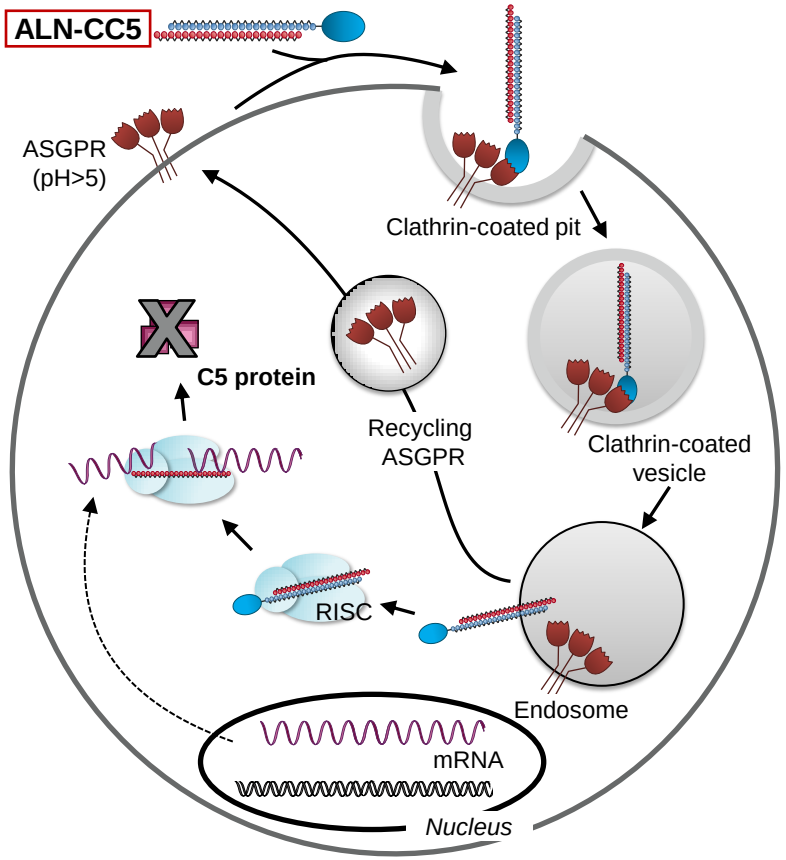


ALN-CC5

- 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

✓: dosing completed

- 50 mg x 1 SC ✓
- 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 ✓
- 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

Ongoing

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

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

ALN-CC5 Phase 1/2: Parts A (SAD) and B (MAD)*
Demographics and Baseline Characteristics

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

	Part A: Single Ascending Dose (SAD) N=4/cohort					Part B: Multiple Ascending Dose (MAD) N=4/cohort					
	50 mg	200 mg	400 mg	600 mg	900 mg	100 mg qW x 5	200 mg qW x 5	400 mg qW x 5	600 mg q2W x 7	200 mg qW x 5, q2W x 4	200 mg qW x 5, qM x 2
Age (years), Mean (Min, Max)	23.8 (20, 26)	22.5 (21, 24)	22.0 (20, 27)	28.5 (23, 38)	26.8 (22, 33)	33.8 (24, 39)	28.0 (24, 32)	25.0 (20, 30)	28.0 (24, 32)	25.0 (23, 30)	24.5 (19, 30)
Gender: Male (%)	100%	100%	75%	0%	50%	75%	25%	50%	50%	75%	50%
BMI (kg/m^2), Mean	24.08	22.35	21.38	24.80	23.53	24.55	23.68	25.48	22.68	23.50	26.65
Race (%)											
- Asian	0%	0%	25%	50%	0%	0%	0%	0%	0%	0%	0%
- Black/African	25%	50%	0%	0%	25%	0%	0%	0%	0%	0%	0%
- Caucasian	50%	25%	50%	50%	75%	100%	100%	100%	100%	75%	100%
- Other	25%	25%	25%	0%	0%	0%	0%	0%	0%	25%	0%
Time on study, Mean (days)	115	286	211	293	258	316	267	219	156	125	112

*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

AE by Preferred Term	Part A: Single Ascending Dose (SAD) N=4/cohort, randomized to ALN-CC5 or placebo (3:1)					
	50 mg	200 mg	400 mg	600 mg	900 mg	All dosing Cohorts N=20
Nasopharyngitis	0	2	2	1	0	**5 (25%)**
Headache	0	1	0	2	2	**5 (25%)**
Nausea	0	0	0	3	0	**3 (15%)**
Influenza-like illness	0	0	0	1	1	**2 (10%)**
Injection site pain	0	0	0	2	0	**2 (10%)**

*Data transfer: 3/2/2016

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

AE by Preferred Term	Part B: Multiple Ascending Dose (MAD) N=4/cohort, randomized to ALN-CC5 or placebo (3:1)						
	100 mg qW x 5	200 mg qW x 5	400 mg qW x 5	600 mg q2W x 7	200 mg qW x 5, q2W x 4	200 mg qW x 5, qM x 2	All dosing cohorts N=24
Nasopharyngitis	1	3	0	3	1	1	**9 (38%)**
Headache	1	1	1	0	0	1	**4 (17%)**

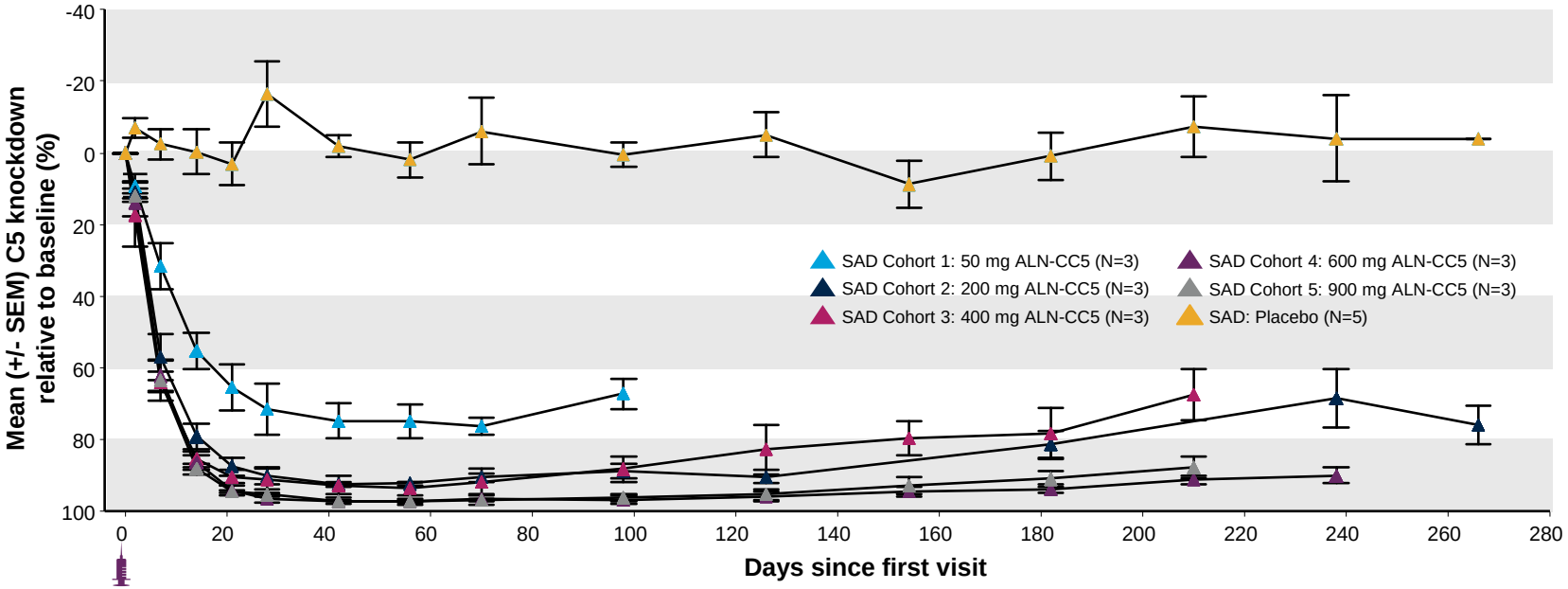
*Data transfer: 3/2/2016

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%



*Data transfer: 03/02/2016

ALN-CC5 Phase 1/2: Part A – SAD*

Summary of Preliminary Results

	Part A: Single Ascending Dose (SAD) Single subcutaneous injection					
	50 mg	**200 mg**	**400 mg**	**600 mg**	**900 mg**	**Placebo**
Residual C5						
Mean nadir; mcg/mL ± SEM	15.3 ± 2.5	5.2 ± 0.5	3.8 ± 1.0	2.2 ± 0.8	1.8 ± 0.2	59.6 ± 2.6
Nadir; mcg/mL	10.8	4.3	1.8	1.1	1.4	53.5
C5 knockdown						
Mean max; % ± SEM	78 ± 3.2	93 ± 0.9	95 ± 1.4	98 ± 0.9	98 ± 0.3	14 ± 2.7
Max; %	84	95	97	99	98	20
CAP inhibition						
Mean max; % ± SEM	59 ± 7.3	79 ± 1.2	80 ± 5.7	93 ± 1.3	93 ± 0.7	26 ± 7.6
Max; %	73	81	91	95	94	44
CCP inhibition						
Mean max; % ± SEM	59 ± 6.5	84 ± 1.6	86 ± 3.2	96 ± 0.7	92 ± 1.1	20 ± 5.1
Max; %	72	86	93	97	94	37
Hemolysis inhibition						
Mean max; % ± SEM	35 ± 7.9	41 ± 4.4	48 ±11.9	74 ± 4.2	71 ± 4.7	9 ± 1.4
Max; %	51	47	71	79	78	13

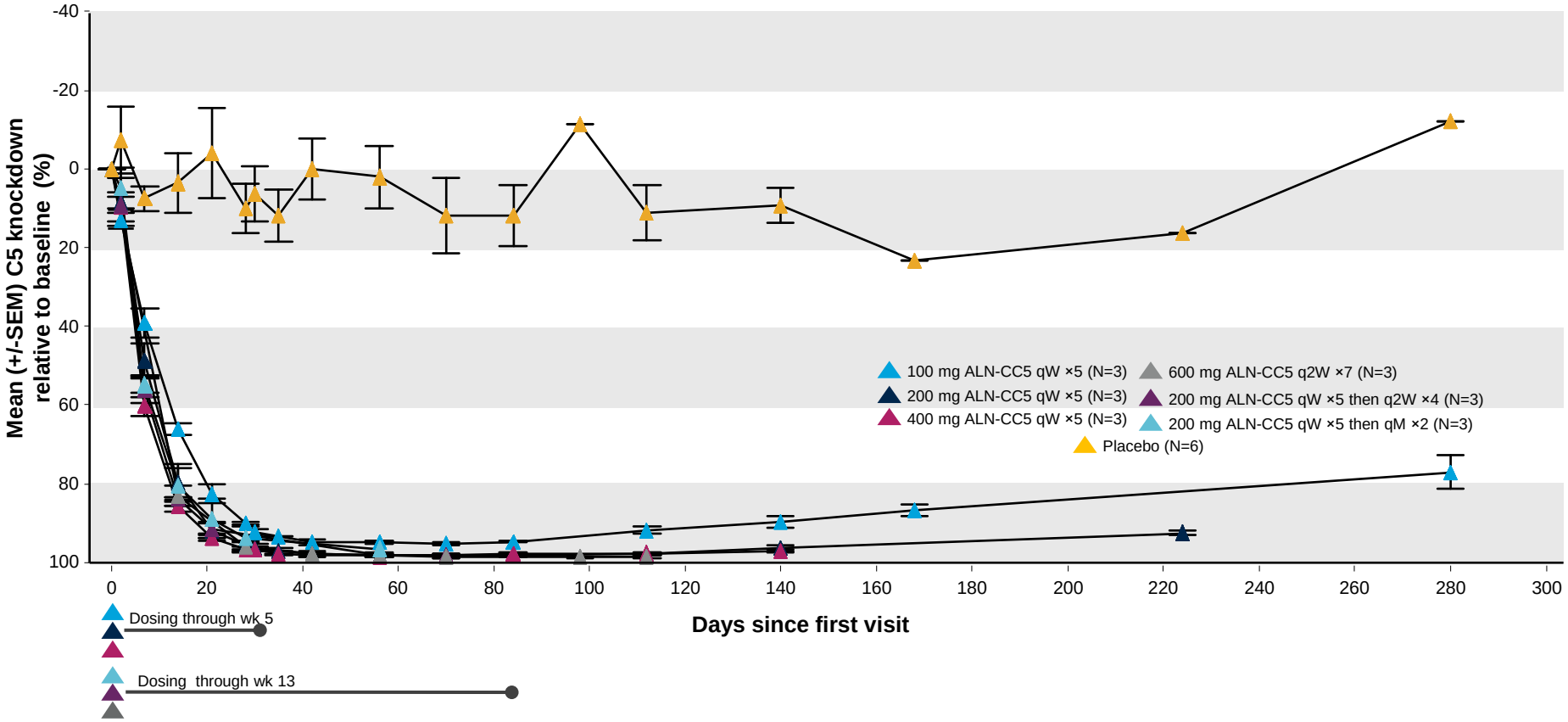
*Data transfer: 03/02/2016 for C5, CAP, CCP; data transfer: 03/14/2016 for hemolysis inhibition

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)



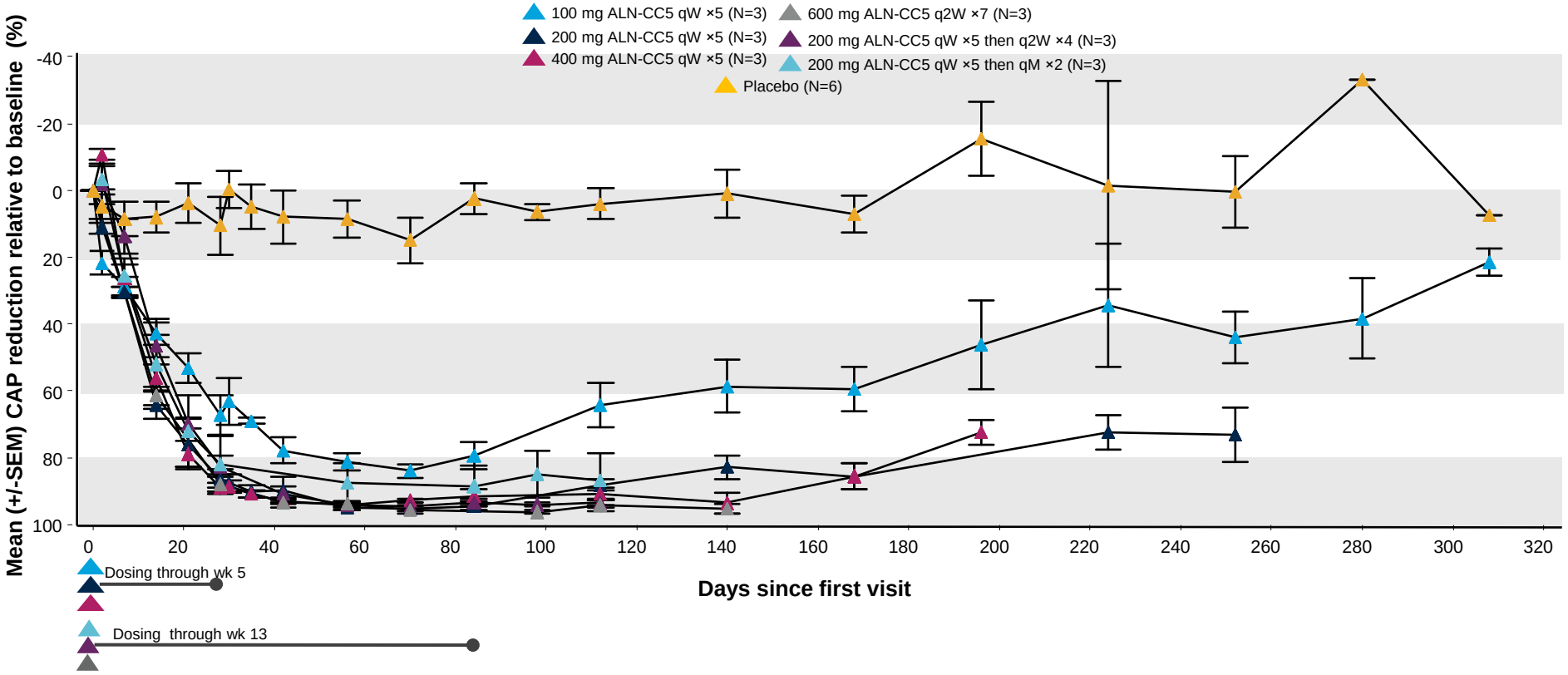
*Data transfer: 03/02/2016

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 subjects[1] in 200mg cohort and above



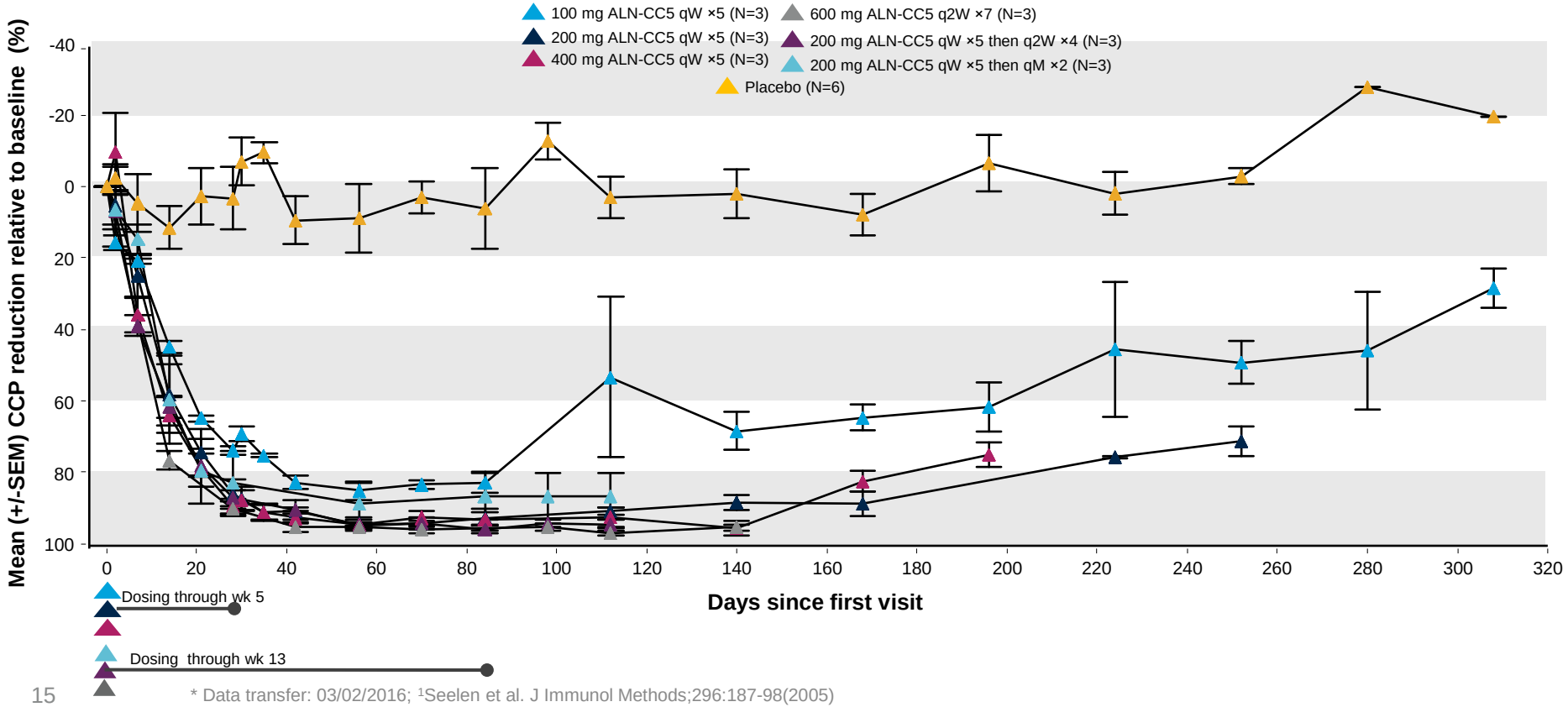
* Data transfer: 03/02/2016; [1]Seelen et al. J Immunol Methods;296:187-98(2005)

ALN-CC5 Phase 1/2: Part B – MAD*

Pharmacodynamics and Clinical Activity: CCP

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



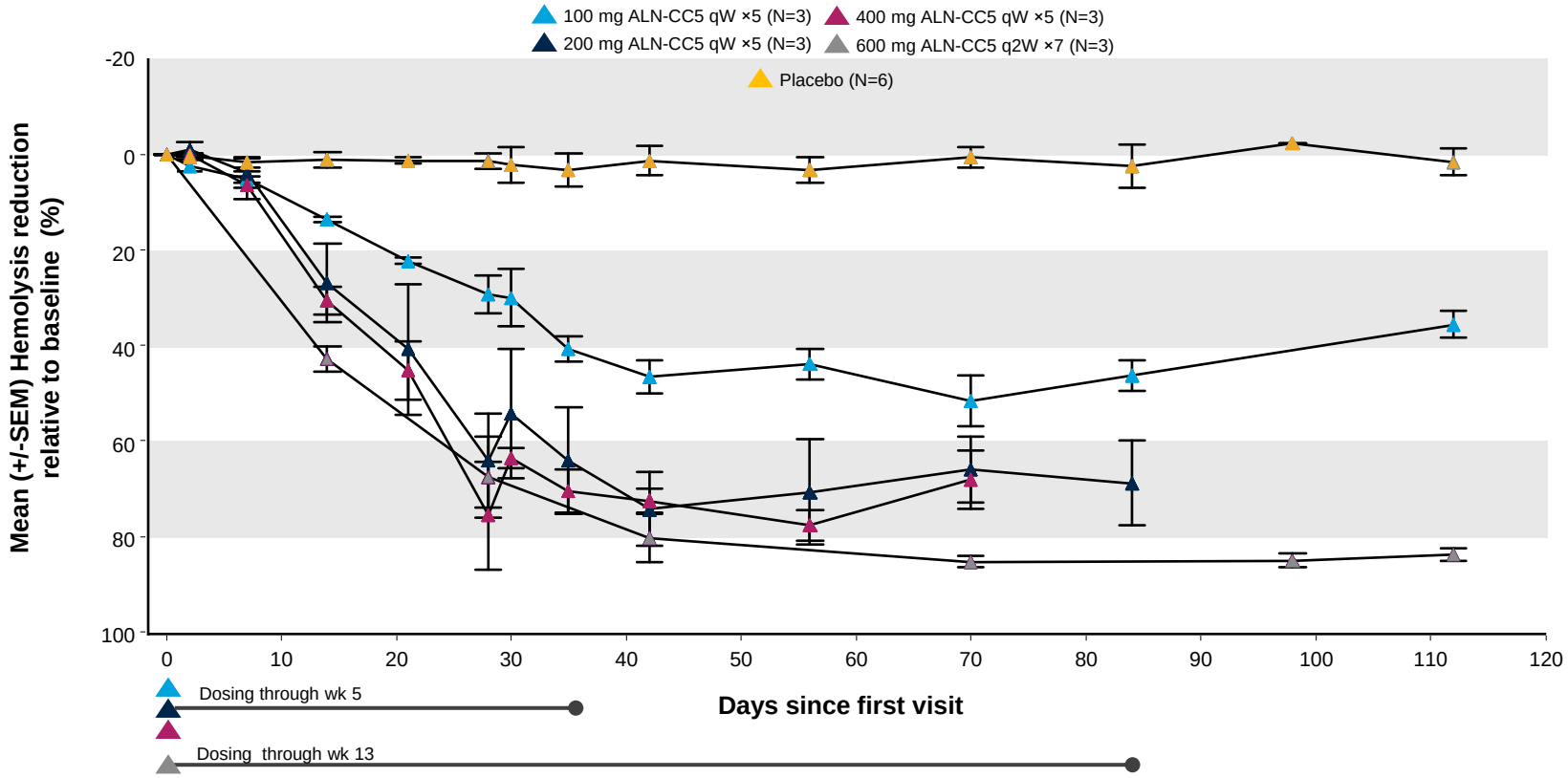
* Data transfer: 03/02/2016; [1]Seelen et al. J Immunol Methods;296:187-98(2005)

ALN-CC5 Phase 1/2: Part B – MAD*

Pharmacodynamics and Clinical Activity: Hemolysis Inhibition

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)



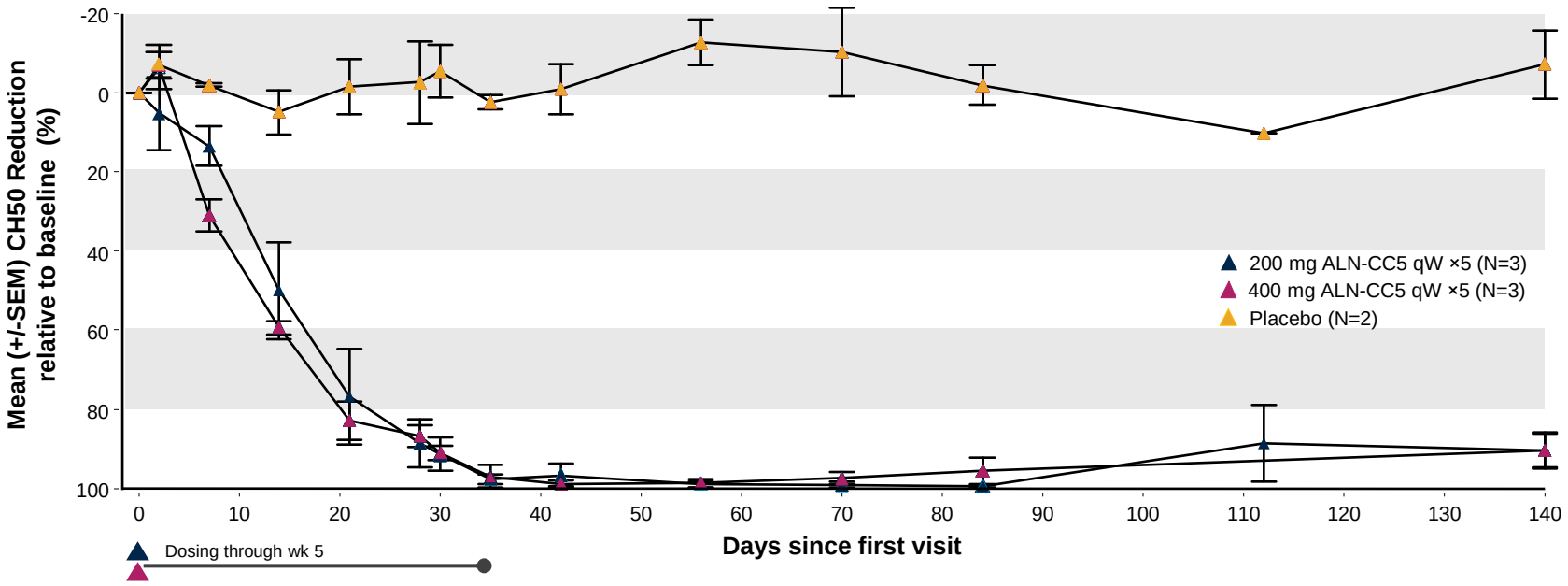
* Data transfer: 03/14/2016

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)



* Data transfer: 03/14/2016

ALN-CC5 Phase 1/2: Part B – MAD*

Summary of Preliminary Results

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

*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

*Data transfer: 03/02/2016 for safety, C5, CAP, CCP; data transfer: 03/14/2016 for hemolysis inhibition

Acknowledgements

Trial participants

Principal investigators

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Thank You

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