Complement blockers

new kids on the block

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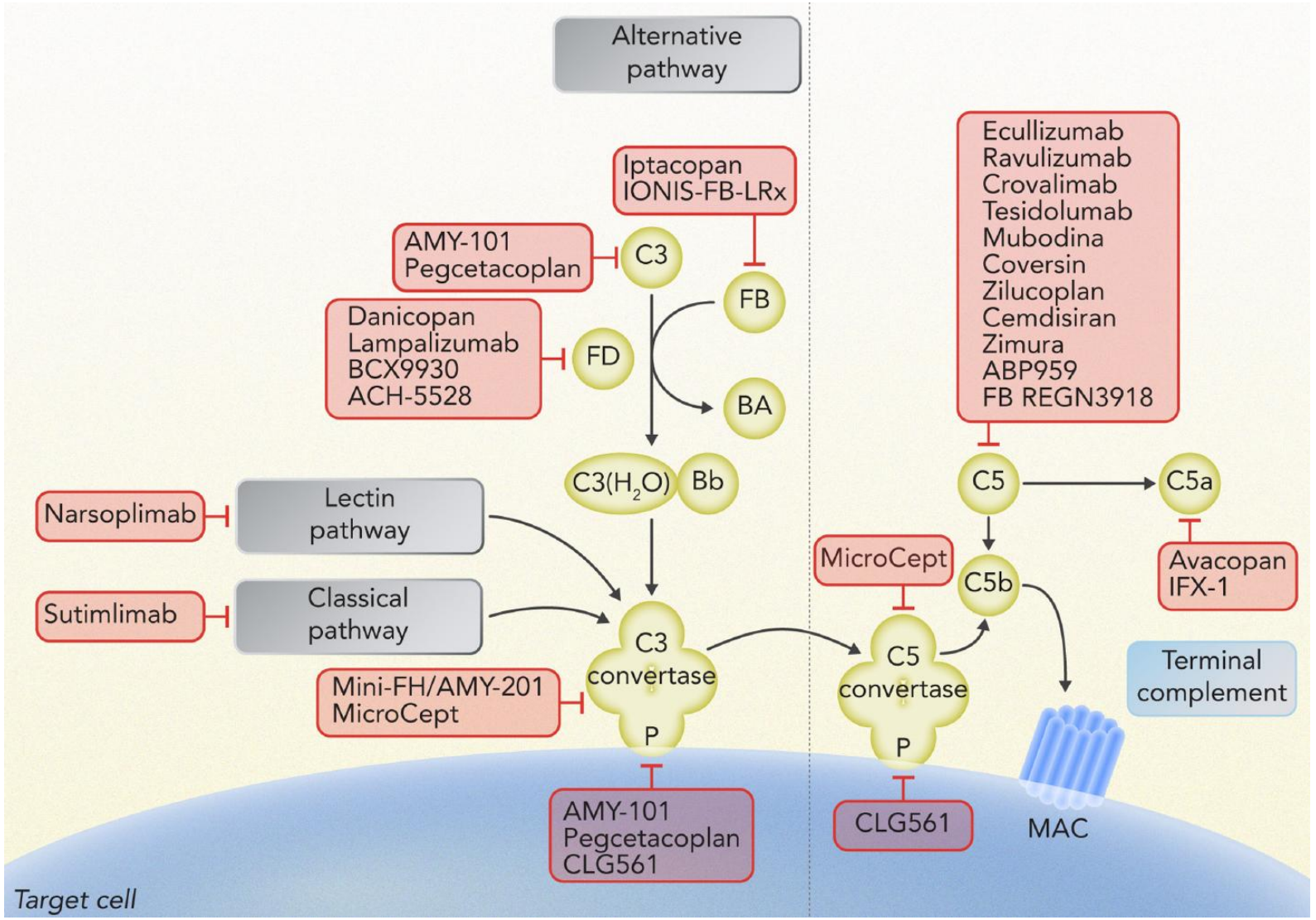
Disclosures

Alexion Pharmaceutical

- Speaker fees
- Travel grant

The pipeline is full and brimming with promise



Gavriilaki Blood 2021

What are the goals to achieve?

- To be at least as efficient as eculizumab
- Less constraints in terms of the route of administration and drug scheduling
- Similar or greater safety profile
- Cheaper

What do we have in the toolbox?

Small molecule inhibitors

- Pegylation or coupling may extend their half-life
- Desired short-term effect
- Oral bioavailability can be achieved

Monoclonal Antibodies

- Highly-specific for their target
- Longer half-life

Small molecule inhibitors

- Lack of specificity
- Off-target effects
- Short half-life *in vivo*

Monoclonal Antibodies

- More expensive
- Low intra-tissue spread

Outlines

1 - Atypical HUS / TMA

2 – C3G

3 - IgAN

4 – Antibody-mediated rejection

5 – Brain death and ischemia reperfusion

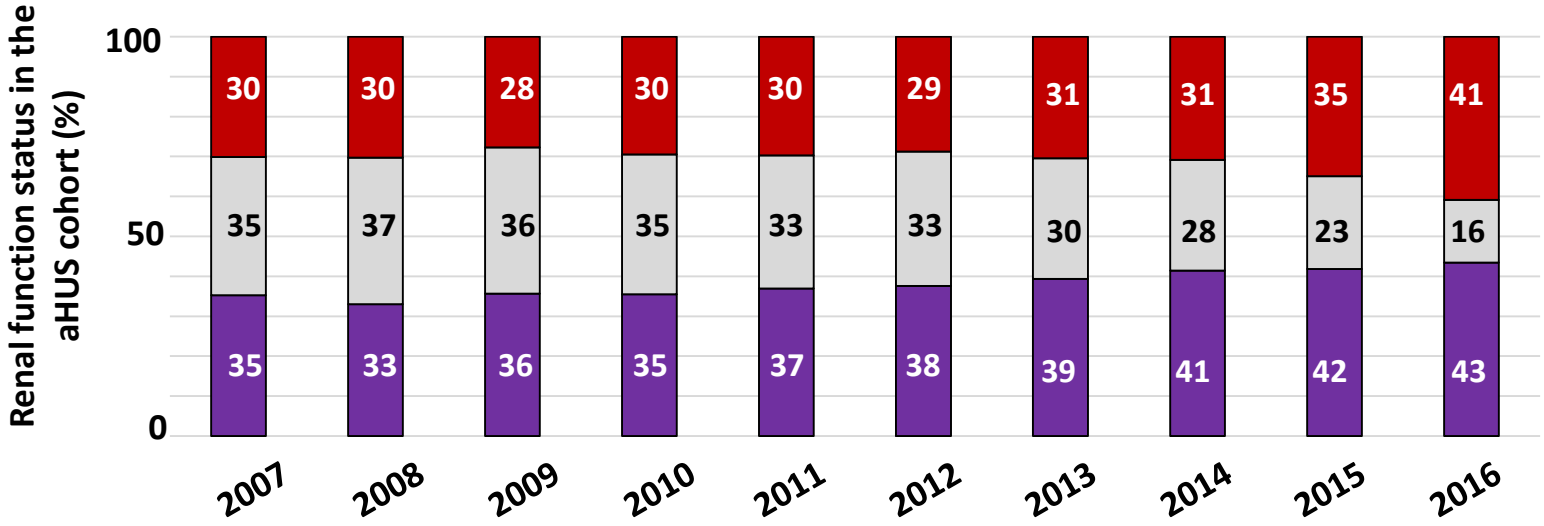
Acknowledgement: Avacopan for ANCA-associated vasculitis is left out in purpose

The aHUS population under chronic dialysis has shrunk during the eculizumab era

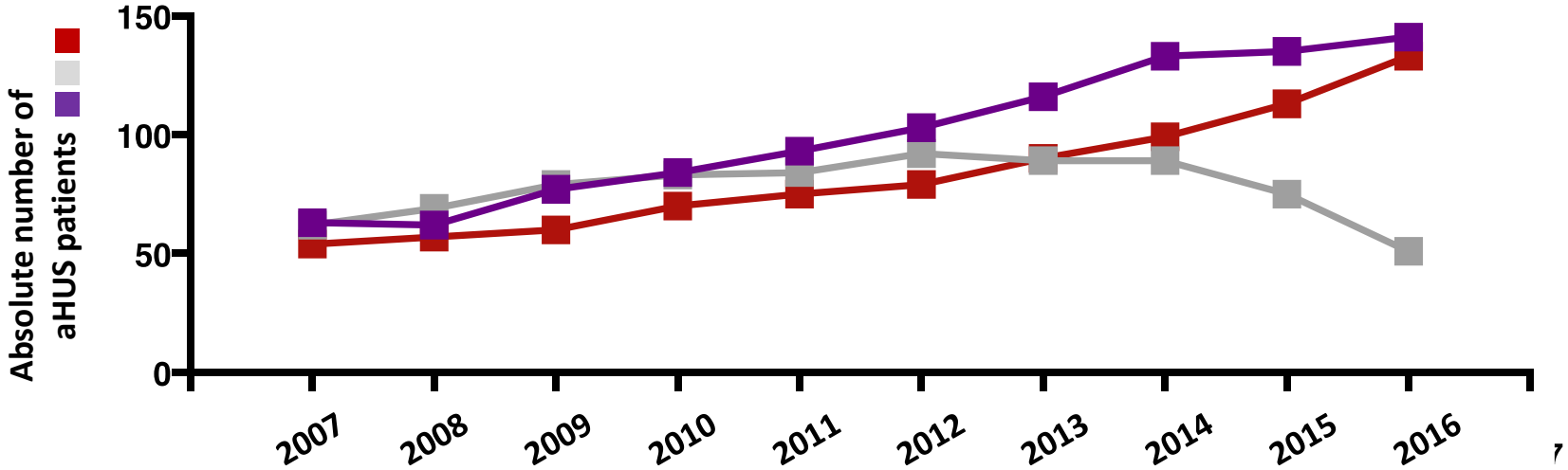
Kidney Transplantation

Dialysis

Native kidneys



Total	179	188	216	237	252	274	295	321	323	325



Zuber JASN 2019

Eculizumab: 10-year pharmacovigilance analysis

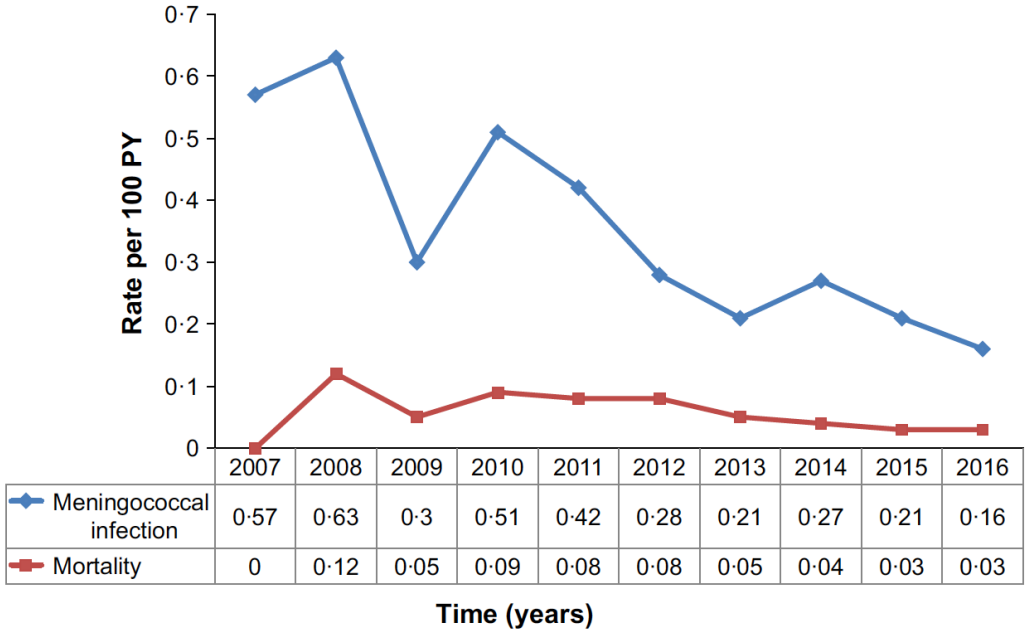
- March **2007** through October **2016**

- Cumulative exposure to eculizumab was **28 518 patient-years**
  - ⇒ PNH: 21 016 PY
  - ⇒ **aHUS: 7502 PY**

- **76 cases of meningococcal infections (0.25/100 PY)**
  - ⇒ PNH: 0.24/100 PY
  - ⇒ **aHUS: 0.29/100 PY**

(**1000 to 2000-fold higher** in patients receiving eculizumab compared with the general population)

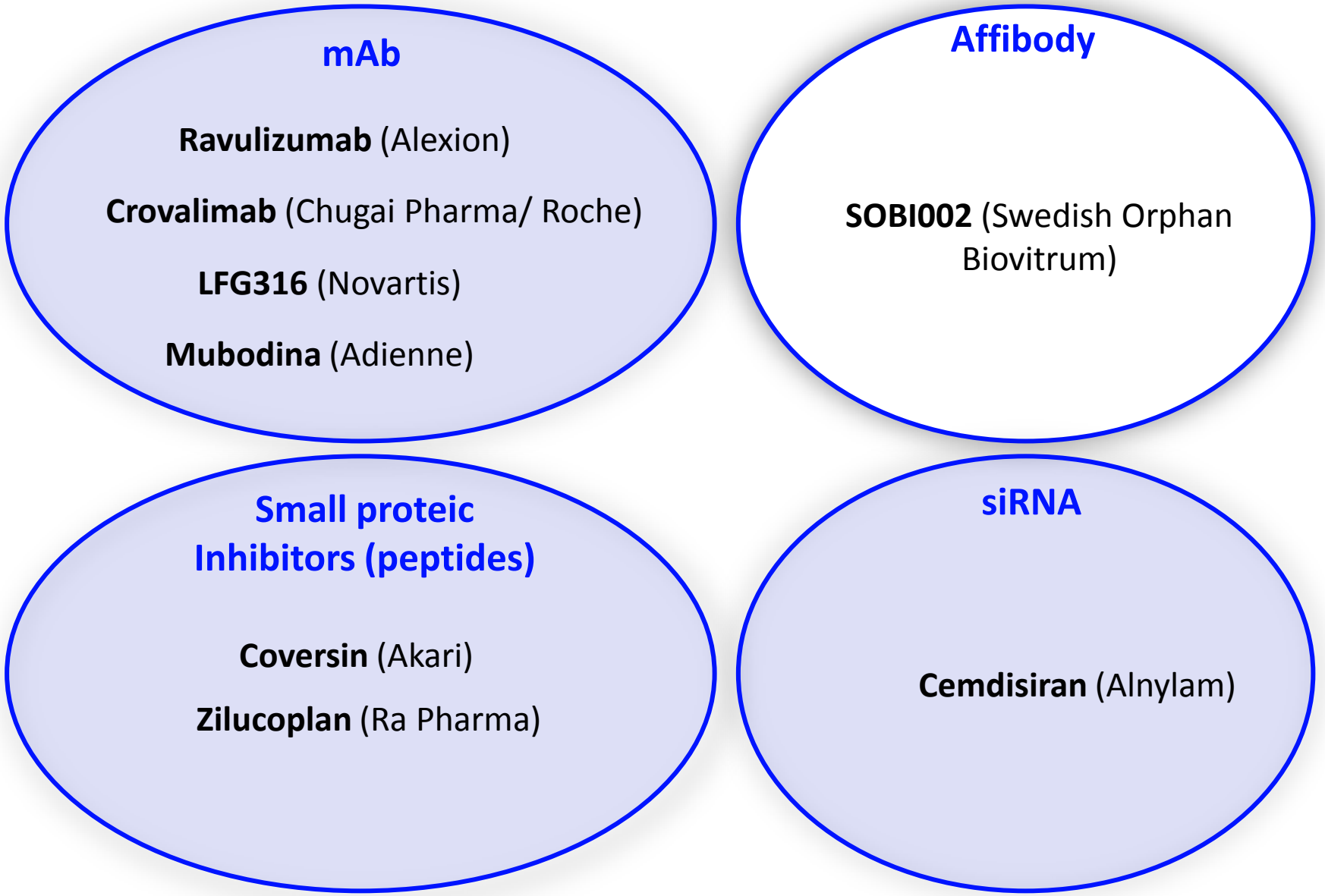
- **8 deaths** related to meningococcal infection



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Meningococcal infection	0·57	0·63	0·3	0·51	0·42	0·28	0·21	0·27	0·21	0·16
Mortality	0	0·12	0·05	0·09	0·08	0·08	0·05	0·04	0·03	0·03

The **rate of meningococcal infections tended to decrease over time**, ranging from 0.57 /100 PY in 2007 to 0.16 /100 PY in 2016

Other C5 blockers



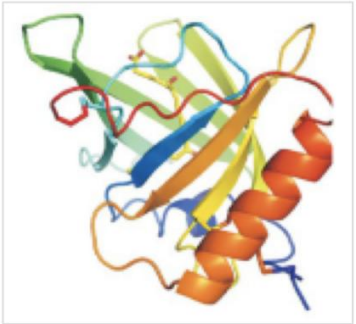
Coversin - Nomacopan

Akari Therapeutics

Ornithodoros moubata

Coversin is a small protein (17kDa) derived from a factor isolated in 2005 from the saliva of the *Ornithodoros moubata* tick.

Prevent the cleavage of C5 by binding the C5 in a different region than eculizumab



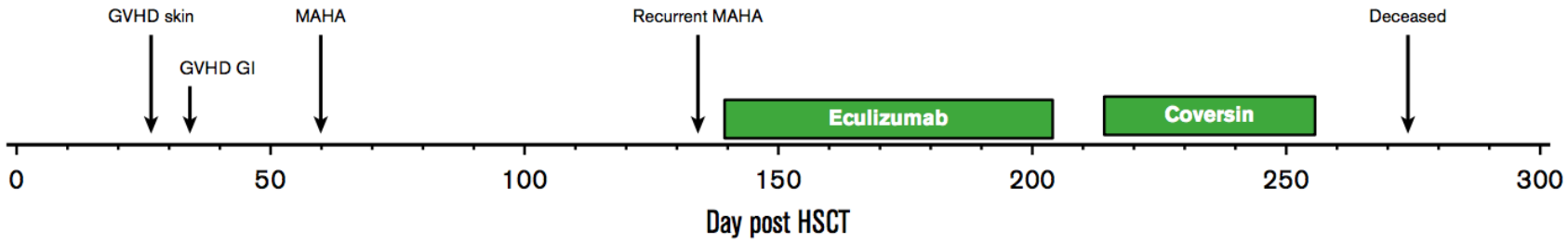
Nomacopan structure

Category	Disease	Preclinical	Phase 1	Phase 2	Phase 3
Pulmonary	COVID-19 pneumonia				
Dermatology	Bullous Pemphigoid				
Hematology	Thrombotic Microangiopathy				
	Paroxysmal Nocturnal Hemoglobinuria				
Ophthalmology	Atopic Kerato-conjunctivitis				
Other	Uveitis Lung				

Coversin - Nomacopan

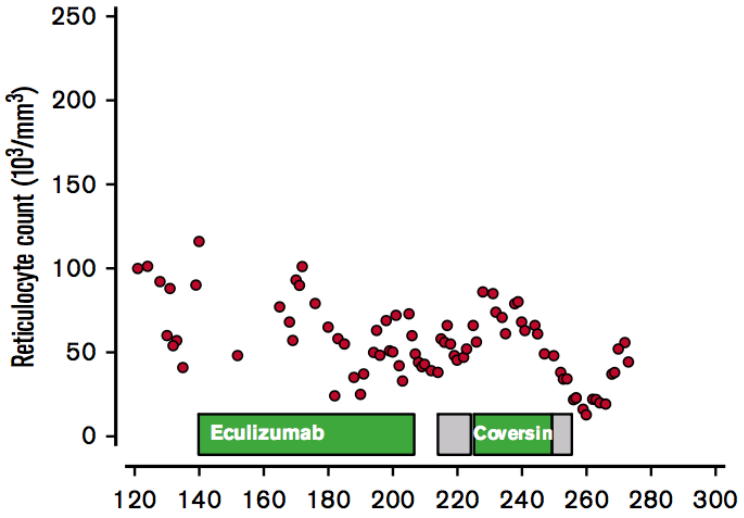
Akari Therapeutics

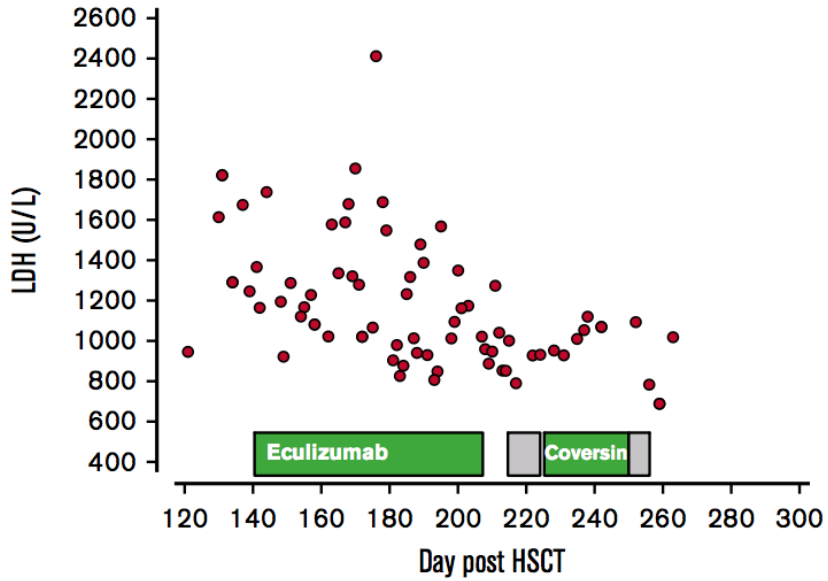
Eculizumab-resistant post-HSCT TMA in a patient with CFH and C5 Arg885His variants



Coversin was administered by daily subcutaneous injection

- **ablating dose of 0.57 mg/kg/day on day 1,**
- **maintenance dose of 0.14 mg/kg/day thereafter.**



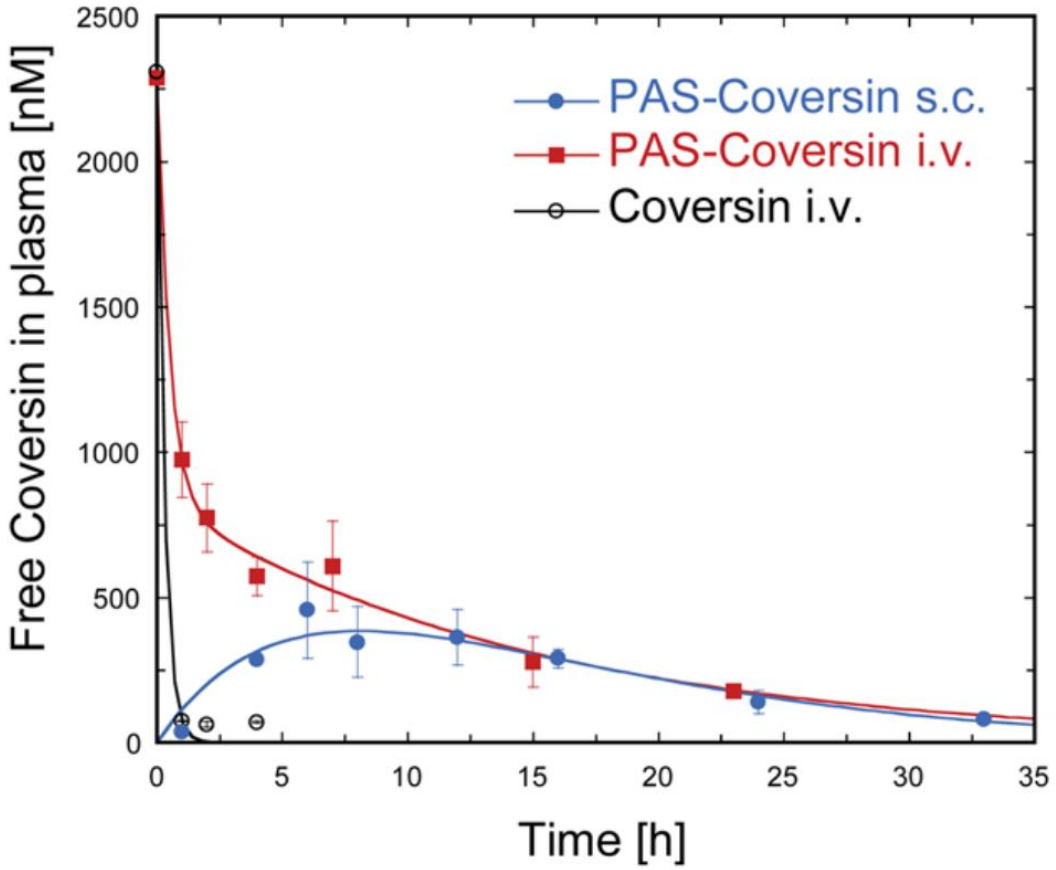


Goodship Blood Adv 2017

PASylated Coversin

Akari Therapeutics

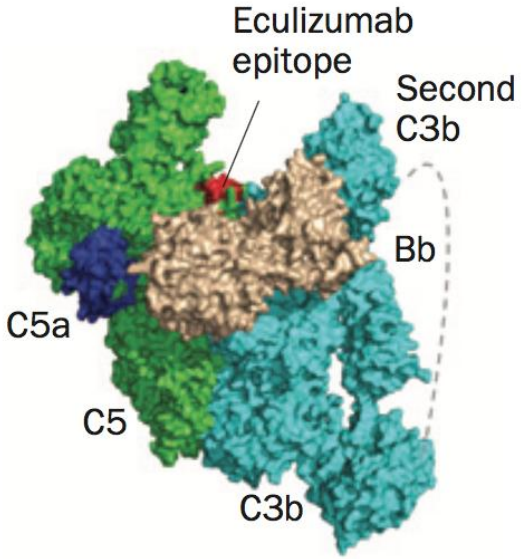
Development of PAS-Coversin is underway. Half-life should be extended to a weekly dosing regimen



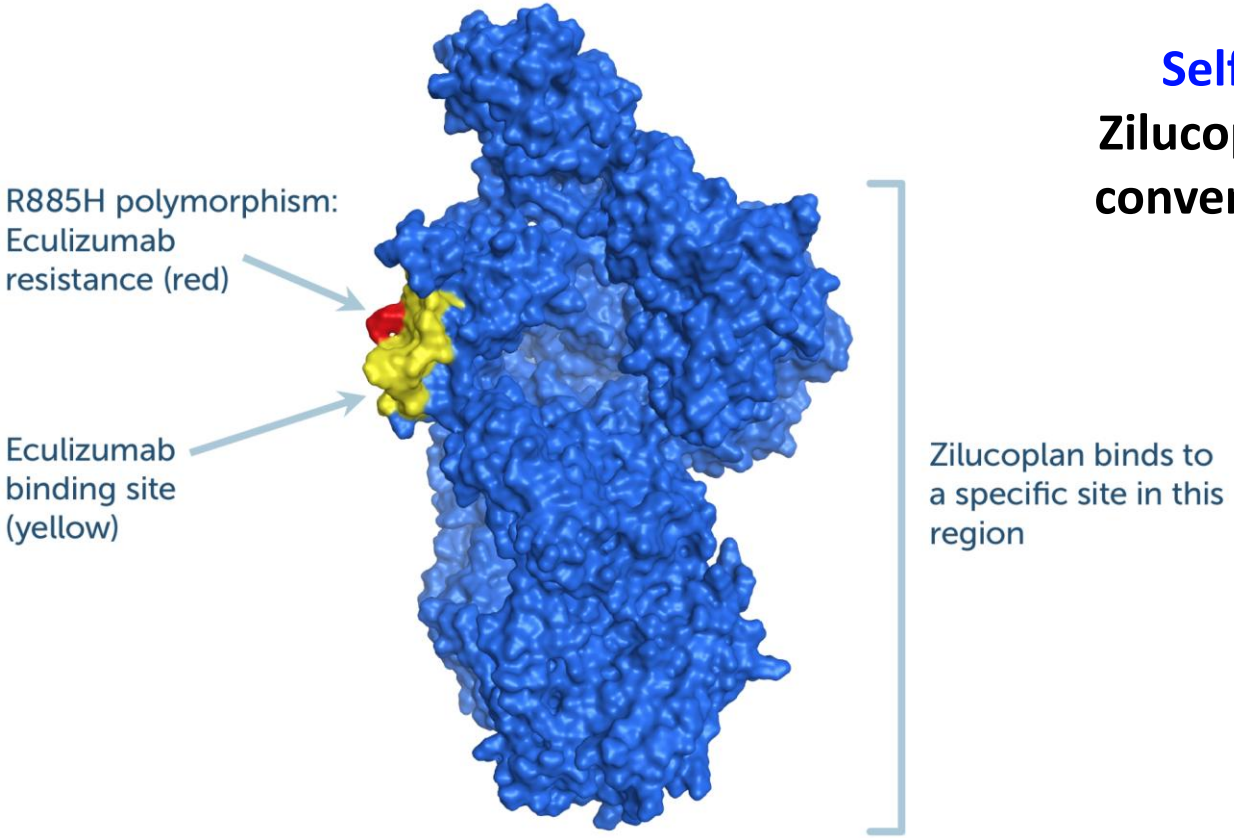
Kuhn Bioconjugate Chem 2016

Zilucoplan

Ra Pharma



Zuber Nat Rev Nephrol 2012



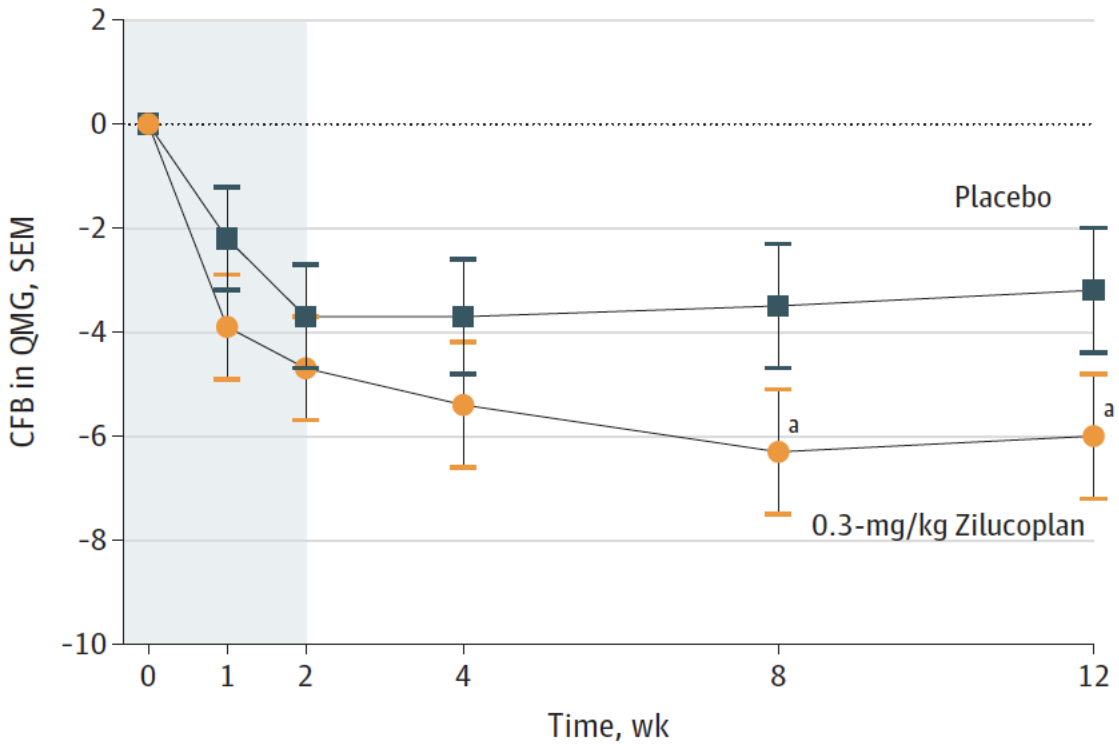
Self-administered SC

Zilucoplan may offer more convenience and flexibility

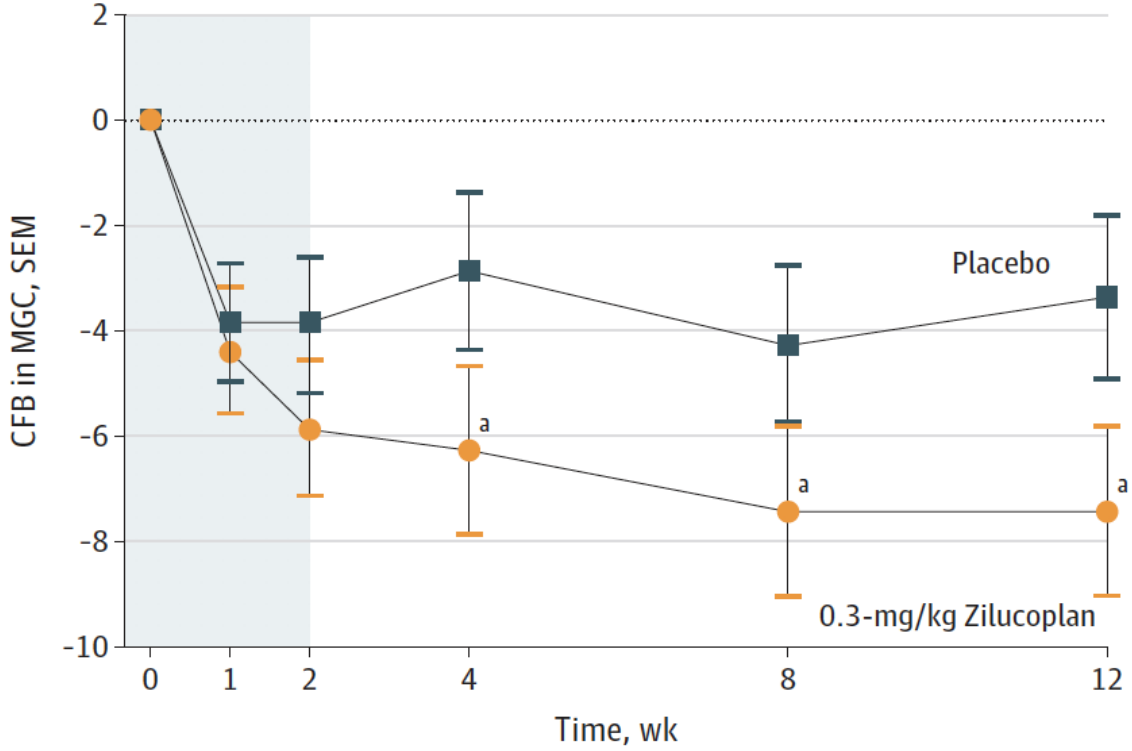
Zilucoplan

Ra Pharma

A QMG **Quantitative Myasthenia Gravis**



D MGC **Myasthenia Gravis Composite**

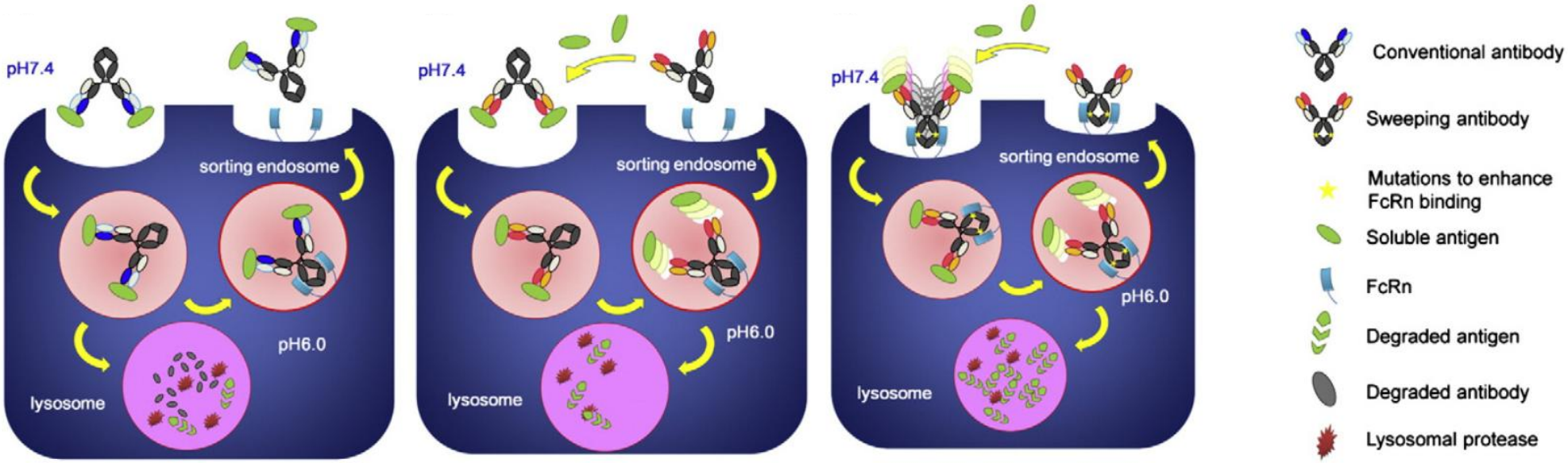


SC administration of zilucoplan (0.3 mg/kg/day) yielded rapid and sustained improvements over 12 weeks in a broad population of patients with moderate to severe AChR-Ab-positive gMG

Howard JAMA Neurology 2020

pH-dependent antigen-binding antibodies

Conventional Antibody | **Recycling Antibody** | **Sweeping Antibody**

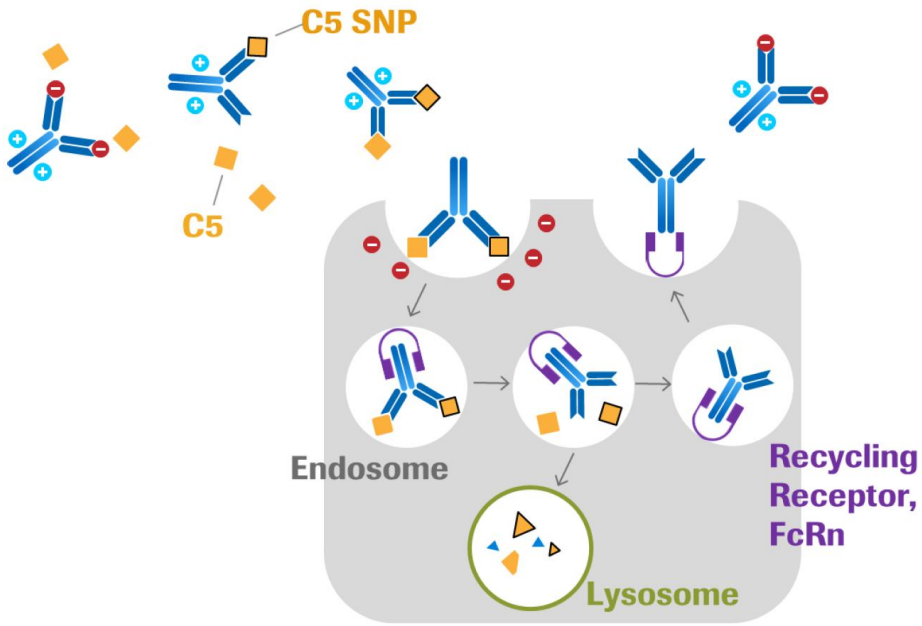


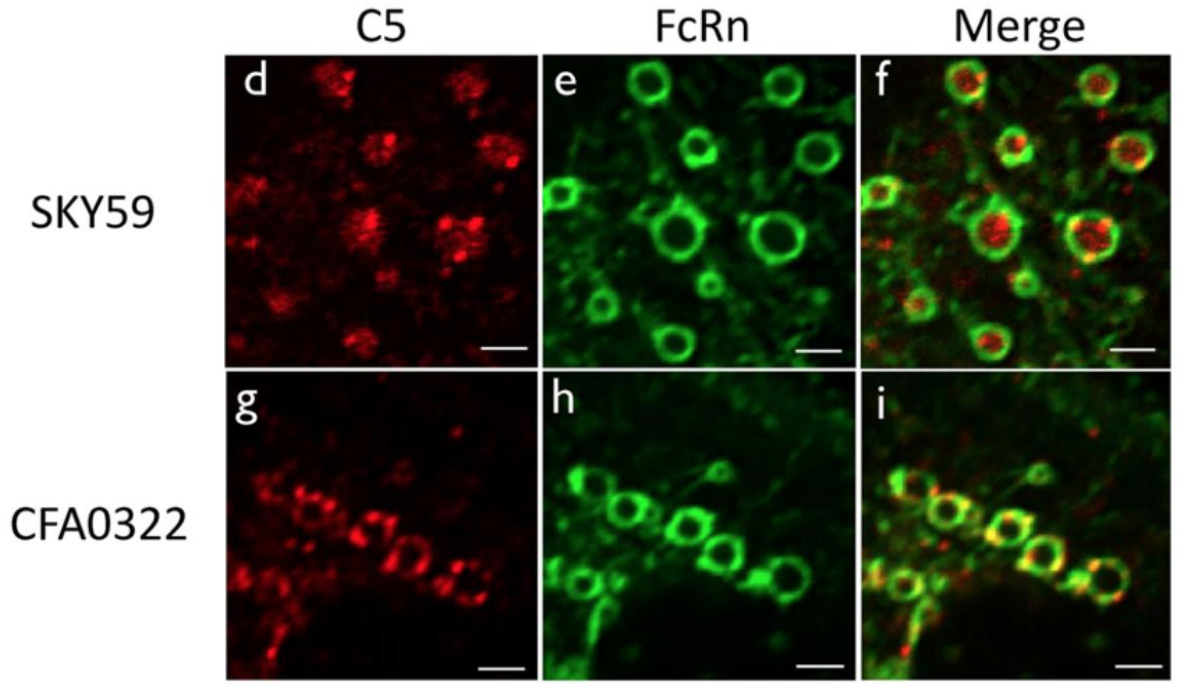
Recycling antibody bound to a soluble antigen in plasma is taken up into cells in the same way as conventional antibody. However, within the sorting endosome, the recycling antibody dissociates the soluble antigen by utilizing its pH-dependent antigen-binding property. The dissociated antigen is transferred to a lysosome and degraded whereas the free antibody is recycled back to the plasma by FcRn

Igawa BAA 2014

SKY59 - Crovalimab

Chugai Pharma/Roche





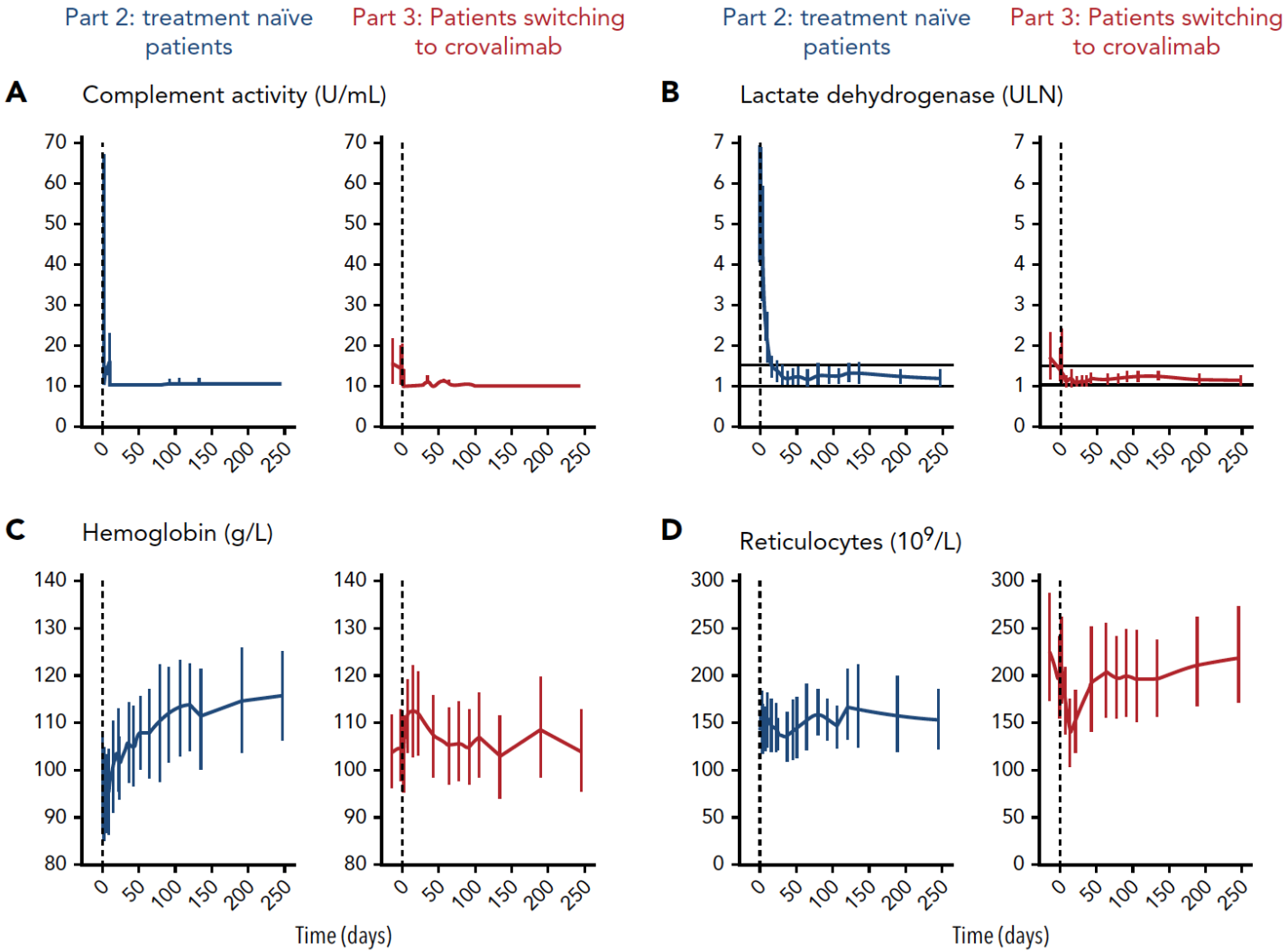
Multidimensional optimization results in a C5-specific antibody with subnanomolar affinity and a 1000-fold lower binding affinity for C5 at pH 5.8.

Administration into cynomolgus monkeys shows that the pH-dependent binding property contributes to the prolongation of the half-life of the C5 antibody.

Fukuzawa Sci Rep 2017

SKY59 - Crovalimab

Chugai Pharma/Roche



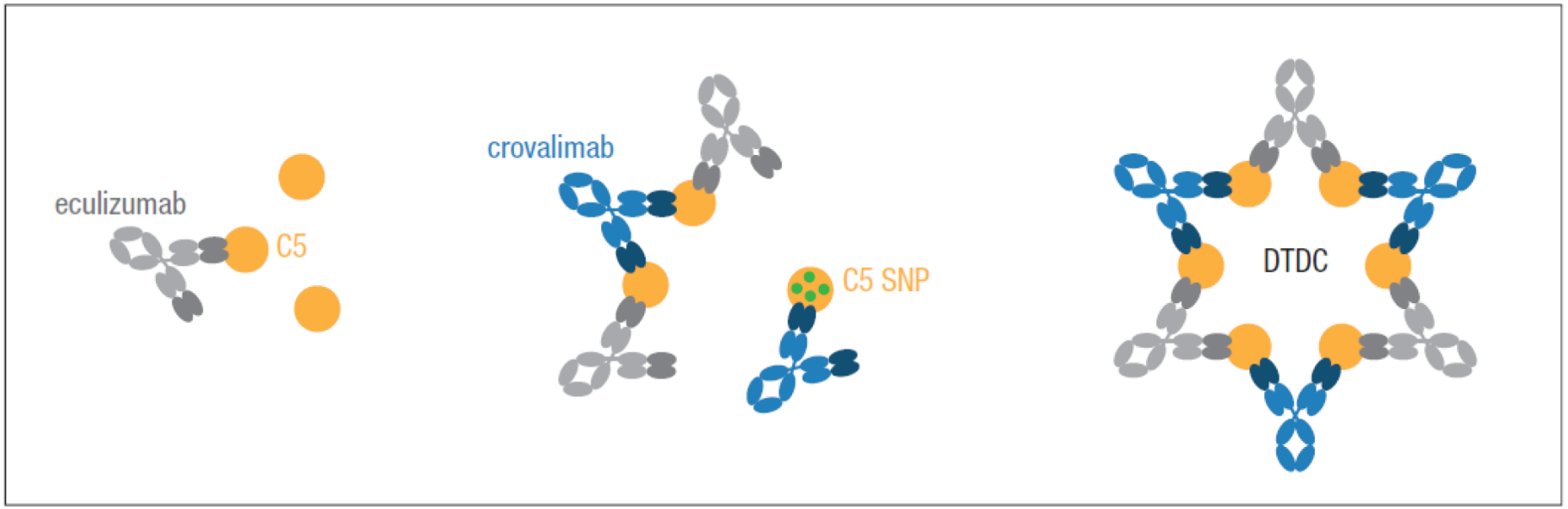
PNH

Subcutaneous crovalimab (680 mg; 4 mL) administered once every 4 weeks, provides complete and sustained terminal complement pathway inhibition and suppressed hemolytic activity

Röth Blood 2020

SKY59 - Crovalimab

Chugai Pharma/Roche



Drug-target-drug complexes (DTDCs) are expected to develop if patients are exposed to crovalimab and eculizumab simultaneously during a switch period

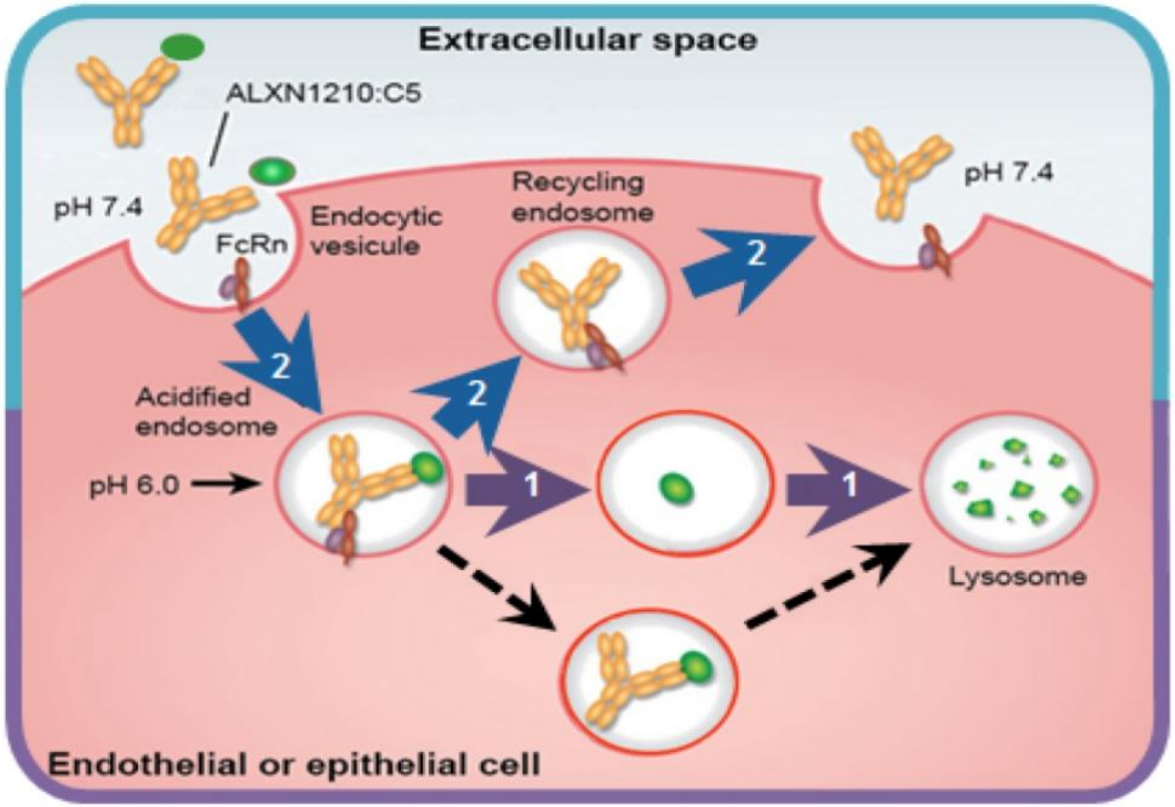
DTDCs of crovalimab, C5 and eculizumab of different sizes were detected in all 19 patients switching to crovalimab, manifesting as transient mild or moderate vasculitis skin reactions in 2/19, but not in any of the treatment-naïve patients.

Röth Blood 2020

Ravulizumab (ALX1210)

Alexion

Ravulizumab (ALXN1210): mechanism of extended duration of action



Substitution of 4 amino acids

As endosomal pH falls below 6.0, the affinity of ravulizumab for C5 weakens (about 36 times), favoring their dissociation, hence minimizing target-mediated drug disposition

At lower endosomal pH, the affinity of ravulizumab for FcRn strengthens (10 fold-increase), increasing the probability of free ALXN1210 recycling back to circulation

3 fold-increased half-life of ravulizumab compared to eculizumab

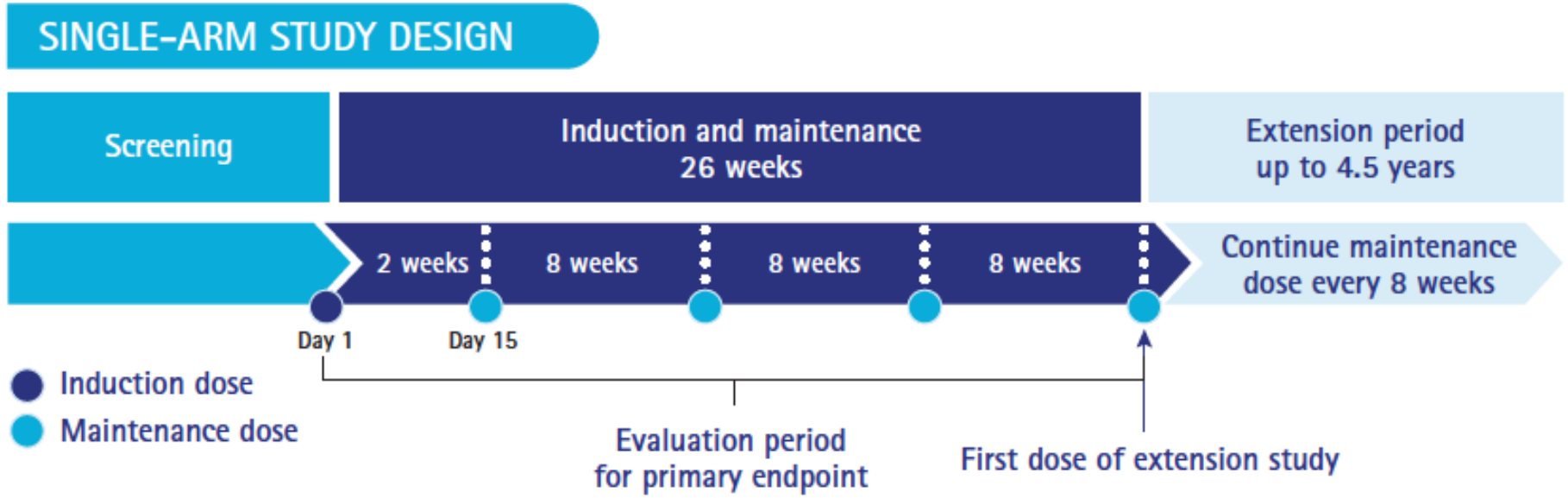
Roth Blood Adv 2018

Ravulizumab (ALX1210)

Alexion

311 Study

Single loading dose on Day 1, followed by regular maintenance dosing (every 8 weeks) beginning on Day 15.



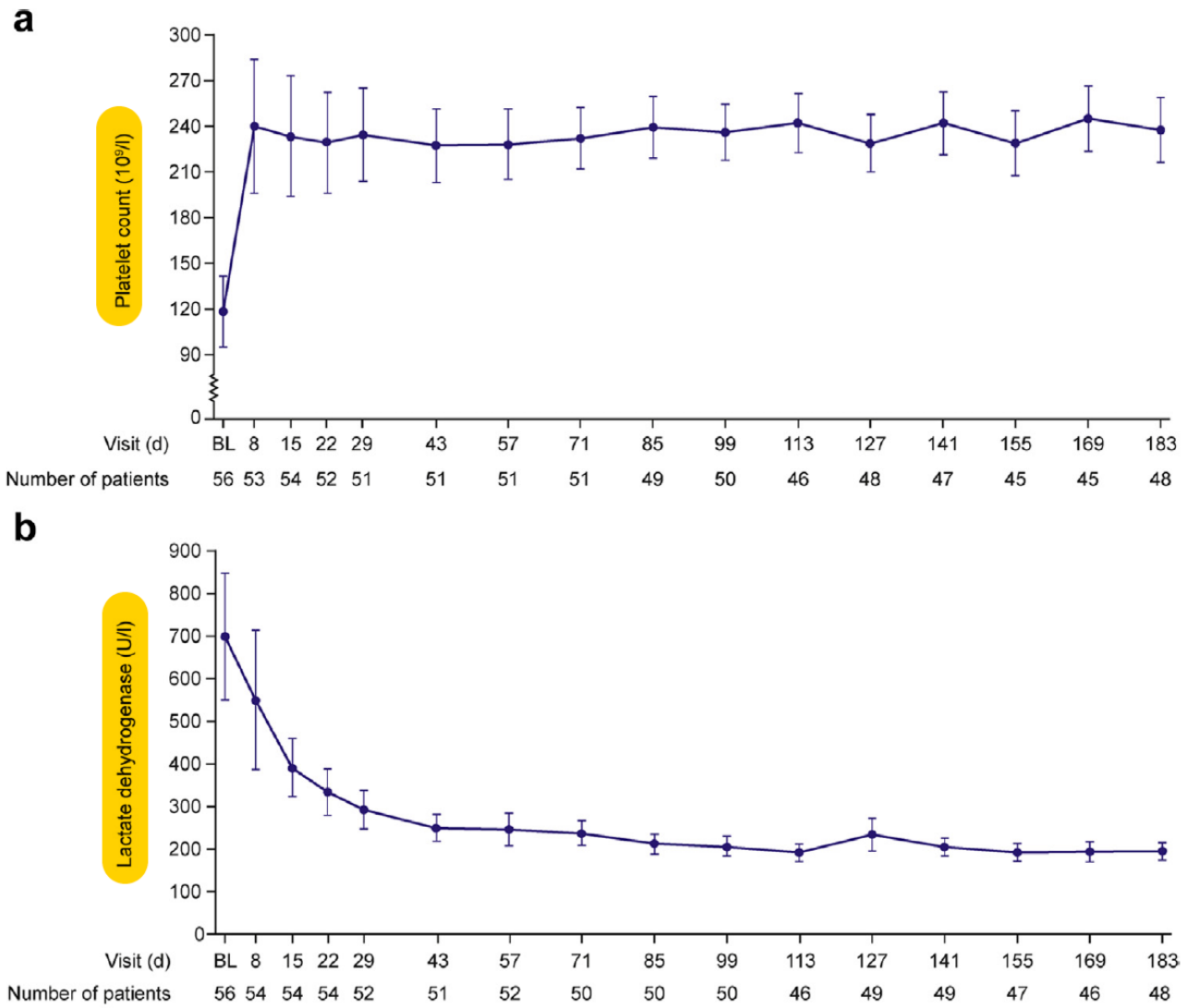
Patient body weight (kg)	Induction phase (mg)	Maintenance phase (mg)
≥40 to <60	2400	3000
≥60 to <100	2700	3300
≥100	3000	3600

Rondeau Kidney Int 2020

Ravulizumab (ALX1210)

Alexion

Prompt and satisfactory hematological response



Rondeau Kidney Int 2020

Ravulizumab (ALX1210)

Alexion

311 Study

Improvement in eGFR (changed to a less severe category between baseline and day 183) was seen in 32 of 47 patients (68.1%).

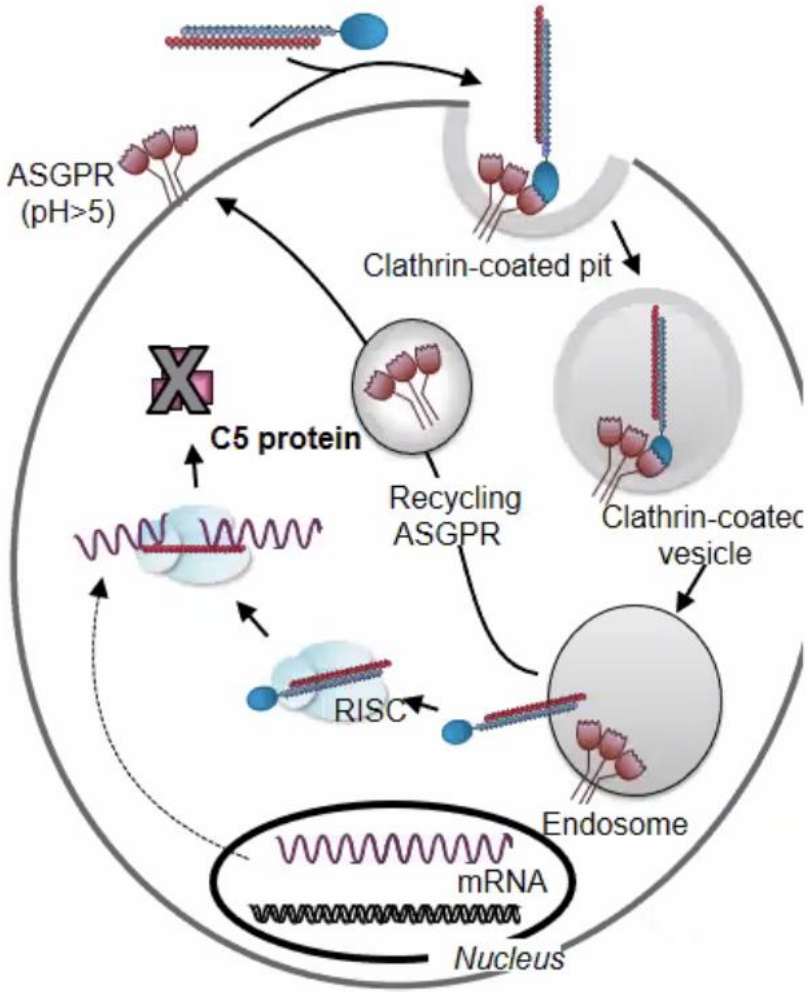
Dialysis was discontinued in 17 of 29 patients (58.6%)

eGFR categories at baseline (N=47)[a]		eGFR categories at day 183					
		1 (≥90)	2 (60–89)	3a (45–59)	3b (30–44)	4 (15–29)	5 (<15)
1 (≥90)	0 (0.0)						
2 (60–89)	3 (6.4)	2 (4.3)	1 (2.1)				
3a (45–59)	1 (2.1)	1 (2.1)					
3b (30–44)	2 (4.3)	2 (4.3)					
4 (15–29)	7 (14.9)	1 (2.1)			3 (6.4)	1 (2.1)	2 (4.3)
5 (<15)	34 (72.3)	6 (12.8)	6 (12.8)	3 (6.4)	3 (6.4)	5 (10.6)	11 (23.4)

Rondeau Kidney Int 2020

Cemdisiran

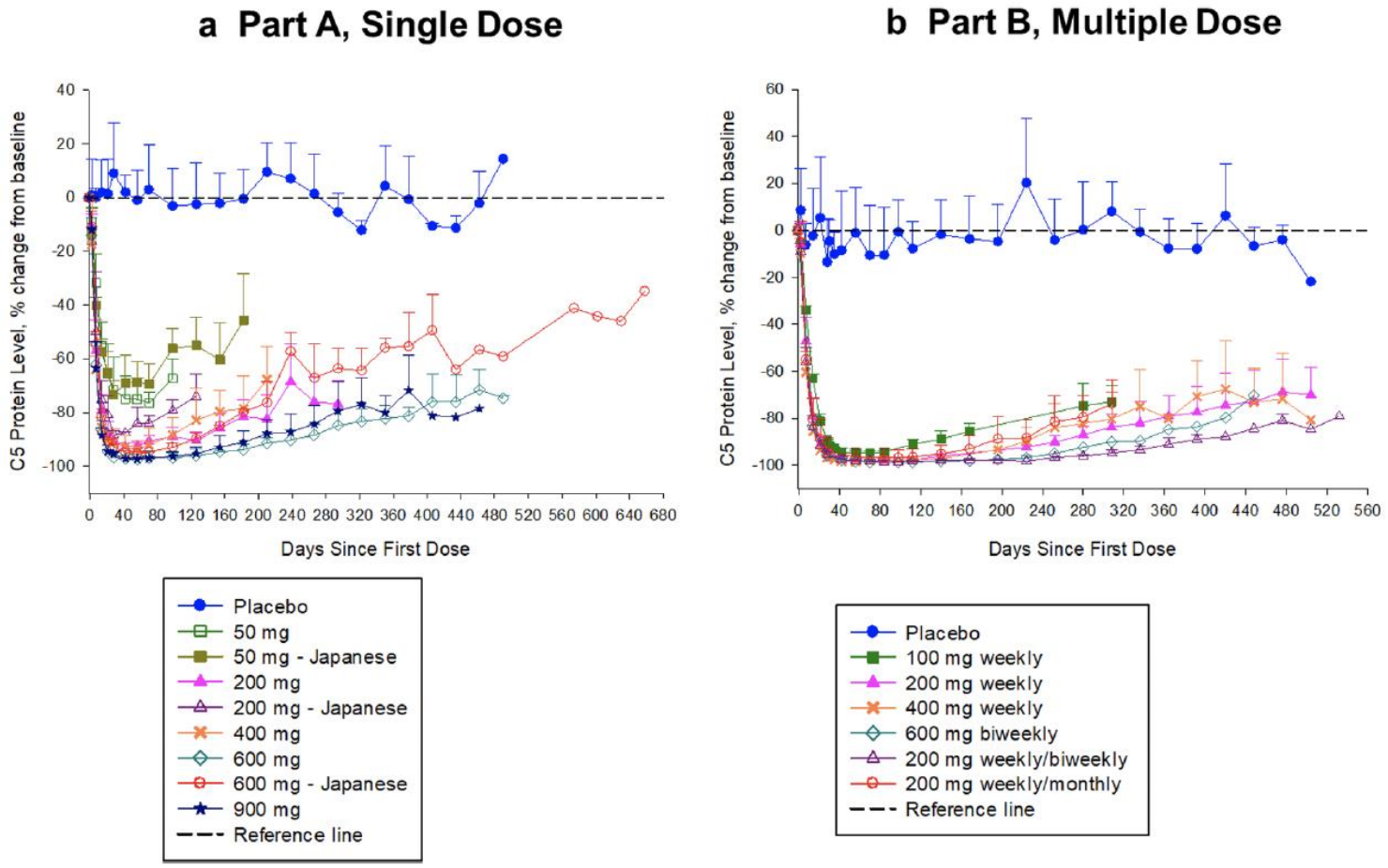
Alnylam Pharmaceuticals



- Double-stranded **siRNA**
- The **sense strand is conjugated to GalNac** for targeted delivery to the liver via binding to ASGPR on hepatocytes
- **Cemdisiran targets a region of C5 mRNA** away from the p.Arg885His mutation
- Once the **anti-sense strand is loaded onto the RISC** (RNA-induced silencing complex), it induces the **cleavage of the complementary messenger RNA**.

Cemdisiran

Alnylam Pharmaceuticals

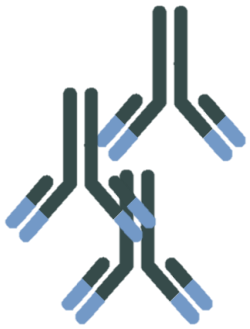


Robust **C5 suppression maintained up to 13 months** following single and multiple doses, which indicates **long residence times of cemdisiran** within hepatocytes

Badri Clinical Pharmacokinetics 2020

Complement alternative pathway inhibitors in aHUS ?

meningococcal vaccine



Lectin Pathway

Classical Pathway

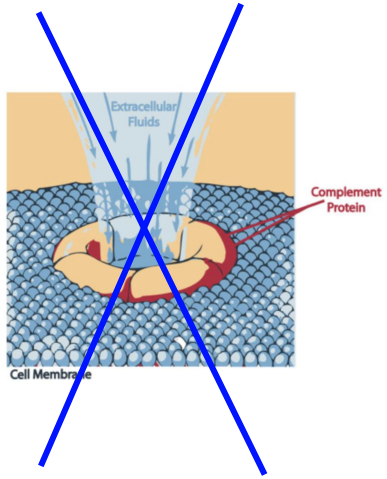
Alternative Pathway

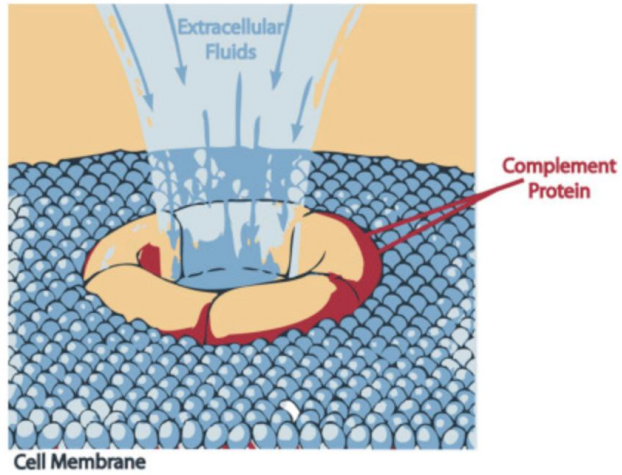
C3

Anti-C5

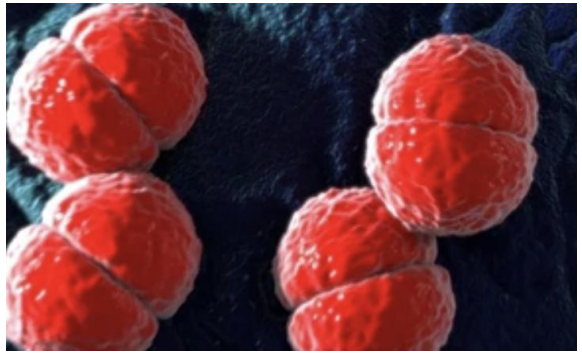
TCC

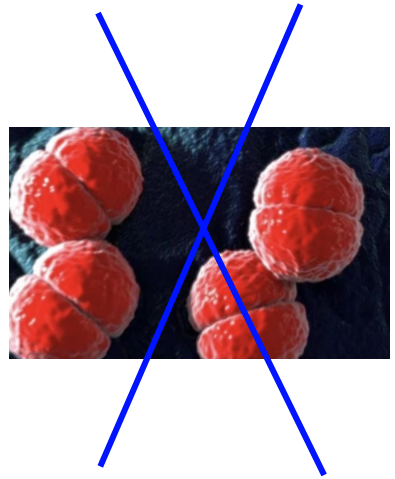
CAP inhibitors





N. meningitidis



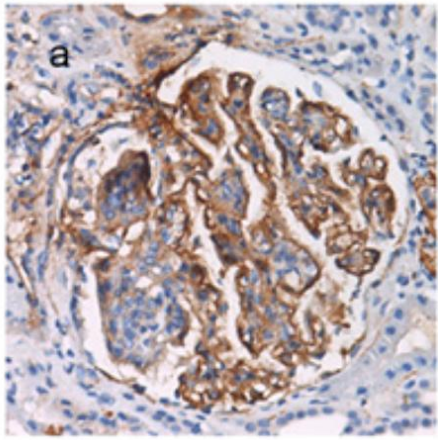


Involvement of the lectin pathway in aHUS/TMA?

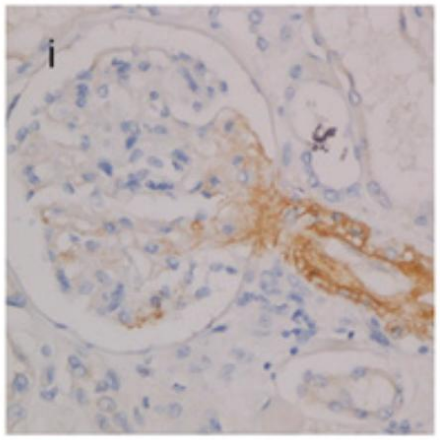
Cases with aHUS had C4d deposits in glomeruli (54.5%) and arterioles (54.5%).

C4d deposits were present in all six samples from patients with HSCT-TMA and were predominantly localized in the glomeruli (100%) and in the arterioles (66.7%)

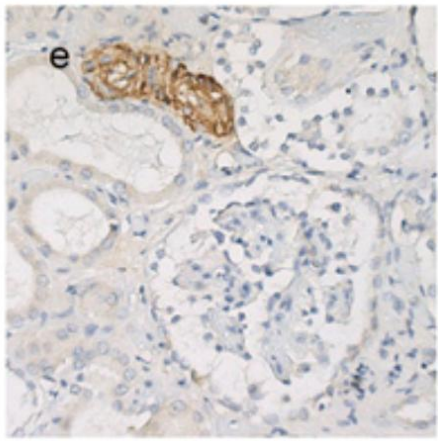
Patient 1



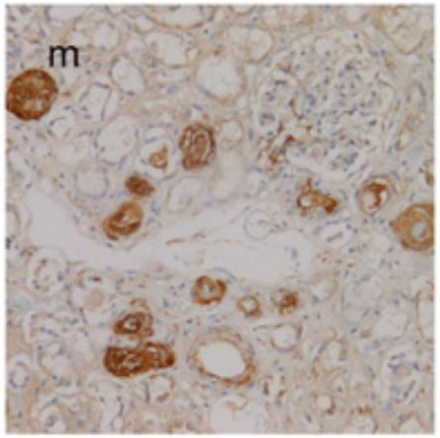
Patient 3



Patient 2



Patient 4

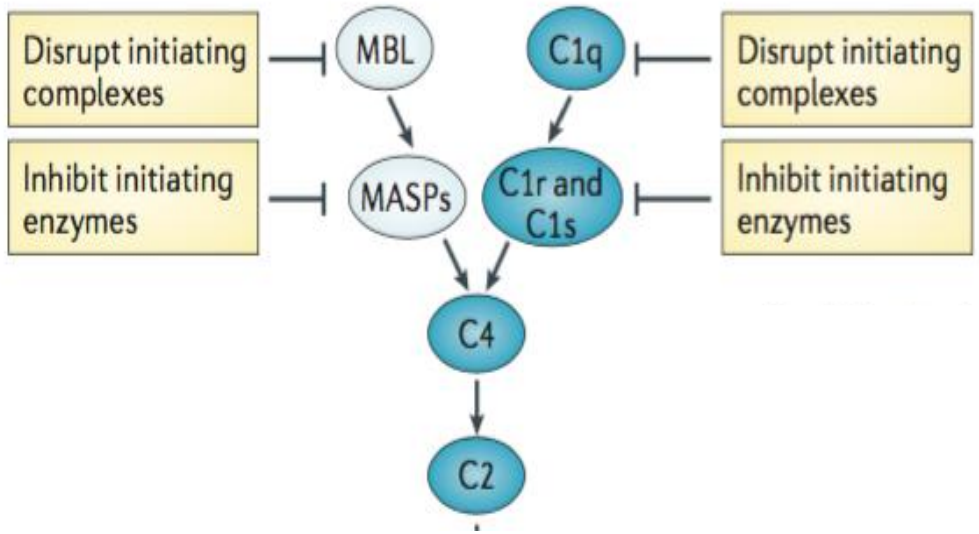


Chua J Am Soc Nephrol 2015

Targeting the enzymes of the initiating complex

Lectin pathway inhibitor

MASP2-blocking human monoclonal antibody (OMS721)



Individuals with loss-of-function mutation in *MBL2* can develop infections of the upper respiratory tract but also may contract more serious infections (pneumonia, meningitis)

Morgan Nat Rev Drug Discov 2015

OMS721 - narsoplimab

Omeros Corporation

Adult TMA

Updated results presented during the 2021 Transplantation & Cellular Therapy Meetings (not yet published)

In a single-arm, open-label, phase 2 trial, investigators enrolled 28 patients to receive narsoplimab IV once weekly for 4 or 8 weeks, along with a 6-week follow-up period.

Findings showed that narsoplimab (OMS721) elicited:

- **61% objective response rate**
- **74% improvement in any organ function**
- **67% improvement in renal function**
- **Narsoplimab was well tolerated**

A Phase 3 trial in aHUS was approved by the FDA (March 2016) and EMA (July 2016), and subsequently launched in February 2017 (*ClinicalTrials.gov Identifier: NCT 03205995*)

ClinicalTrials.gov Identifier: NCT 02222545

OMS721 - narsoplimab

Omeros Corporation

Adult TMA

Toward an expedited development and review of OMS721 in HSCT-TMA

- FDA grants breakthrough therapy designation to OMS721 for the treatment of high-risk HSCT-TMA (April 26 2018)
- European Commission designates OMS721 as an orphan medicinal product for treatment in HSCT (August 28, 2018)
- In January 2021, the FDA granted a priority review designation to a license application for narsoplimab for the treatment of HSCT-TMA. The regulatory agency is expected to make a decision on the application by July 2021.

Antibodies to watch in 2022

Table 4. Investigational antibody therapeutics in regulatory review in the European Union or the United States.

International non-proprietary name	Target; Format	Indication under review	Status in EU	Status in US
Faricimab	VEGF-A, Ang-2; Human/humanized IgG1 /λ bispecific	Diabetic macular edema and neovascular age-related macular degeneration	In review	In review
Sutimlimab	C1s; Humanized IgG4	Cold agglutinin disease	NA	In review (2nd cycle)
Tebentafusp	gp100, CD3; Bispecific immunoconjugate	Metastatic uveal melanoma	NA	In review
Relatlimab	LAG-3; Human IgG4	Melanoma	In review	In review
Sintilimab	PD-1; Human IgG4	Non-small cell lung cancer	NA	In review
Ublituximab	CD20; Chimeric IgG1	Chronic lymphocytic leukemia and small lymphocytic lymphoma; Multiple sclerosis	NA	In review
Tezepelumab	Thymic stromal lymphopoietin; Human IgG2	Severe asthma	In review	In review
Penpulimab	PD-1; Humanized IgG1	Metastatic nasopharyngeal carcinoma	NA	In review
Tislelizumab	PD-1; Humanized IgG4	Esophageal squamous cell carcinoma	NA	In review
Lecanemab	Amyloid beta protofibrils; Humanized IgG1	Early Alzheimer's disease	NA	Rolling BLA in review
Toripalimab	PD-1; Humanized IgG4	Nasopharyngeal carcinoma	NA	In review
Inolimomab	CD25; Murine IgG1	Acute graft-vs-host disease	NA	In review
Omburtamab	B7-H3; Murine IgG1	CNS/leptomeningeal metastasis from neuroblastoma	In review	NA
Spesolimab	IL-36 receptor; Humanized IgG1	Generalized pustular psoriasis	In review	NA
Teplizumab	CD3; Humanized IgG1	Type 1 diabetes	NA	In review (2nd cycle)
Retifanlimab	PD-1; Humanized IgG4	Carcinoma of the anal canal	In review	In review (2nd cycle)
Oportuzumab monatox	EpCAM; Humanized scFv immunotoxin	Bladder cancer	MAA withdrawn	In review (2nd cycle)
Narsoplimab	MASP-2; Human IgG4	Hematopoietic stem cell transplant-associated thrombotic microangiopathy	NA	In review (2nd cycle)
Donanemab	Amyloid β; Humanized IgG1	Early Alzheimer's disease	NA	In review

Kaplon MABS 2022

Outlines

1 - Atypical HUS / TMA

2 - C3G

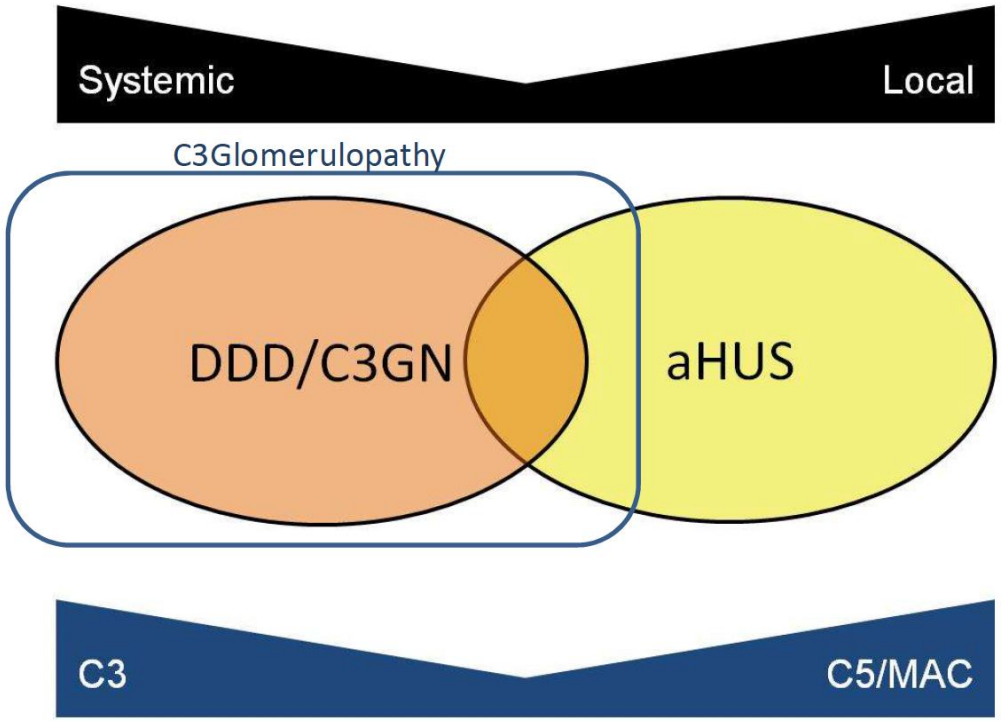
3 - IgAN

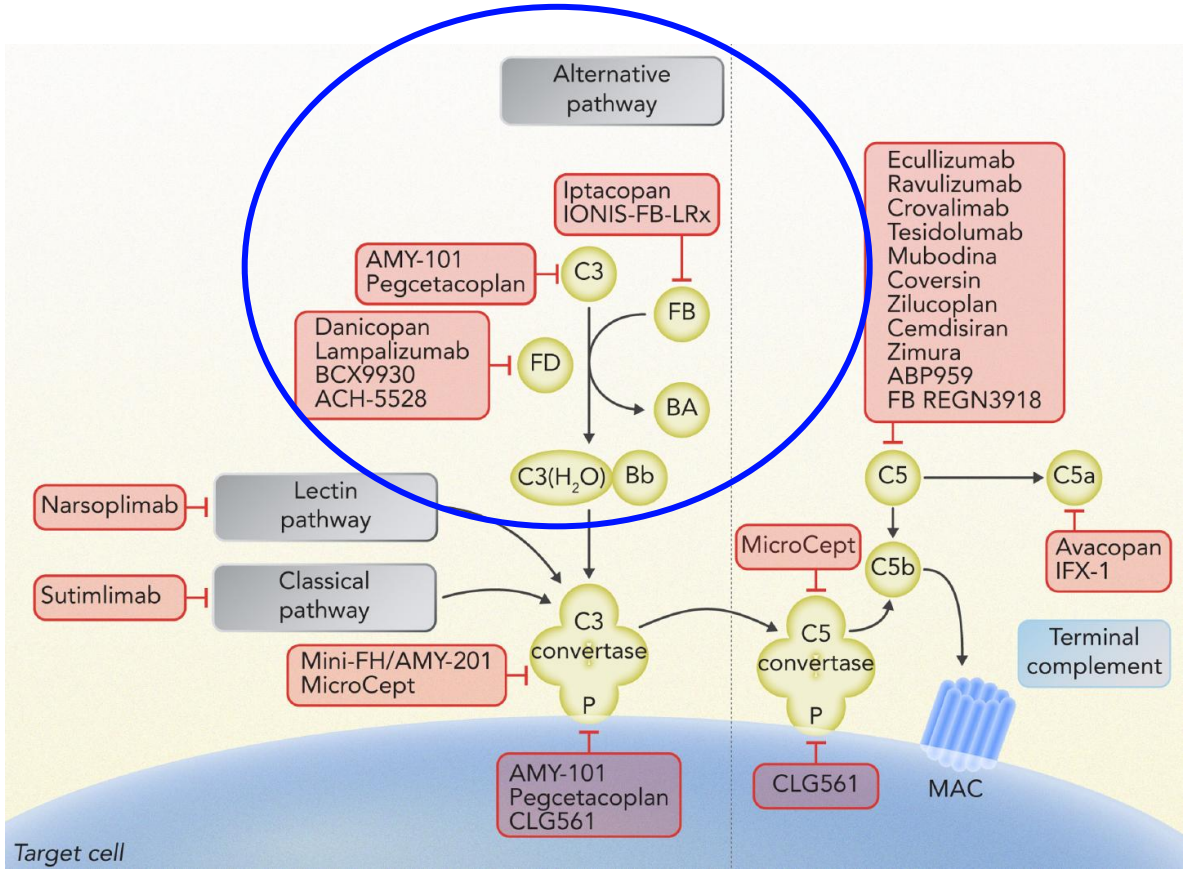
4 – Antibody-mediated rejection

5 – Brain death and ischemia reperfusion

Acknowledgement: Avacopan for ANCA-associated vasculitis is left out in purpose

Targeting the alternative pathway

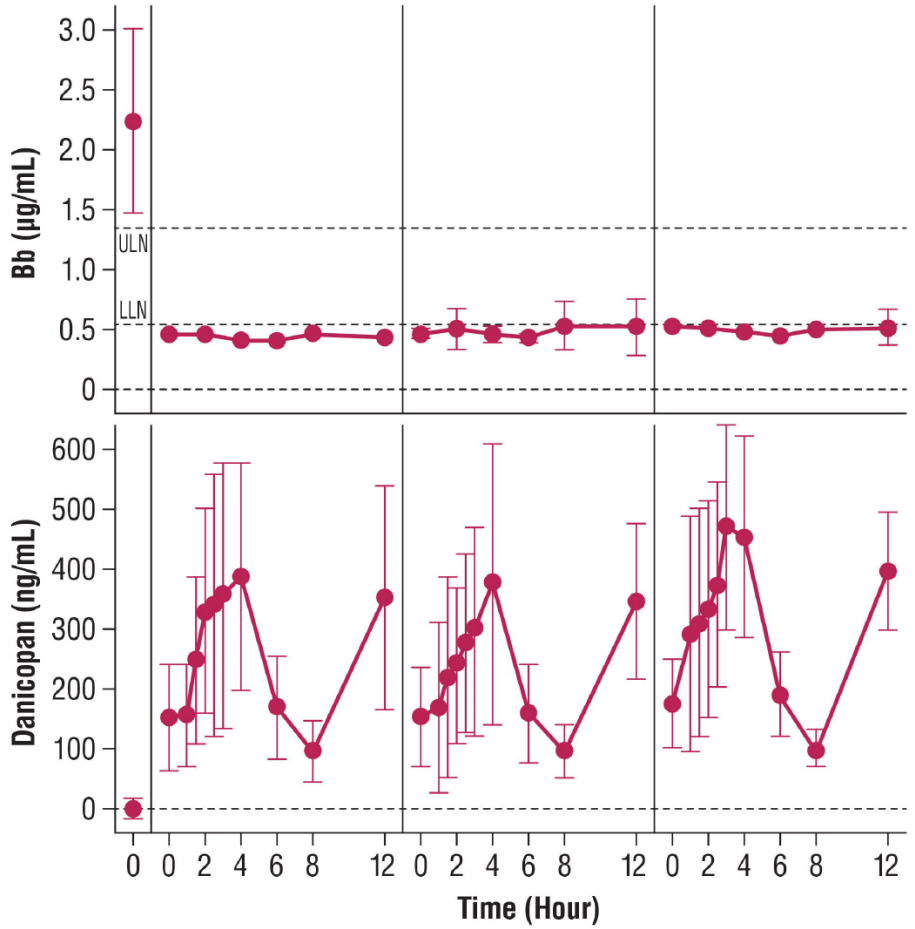


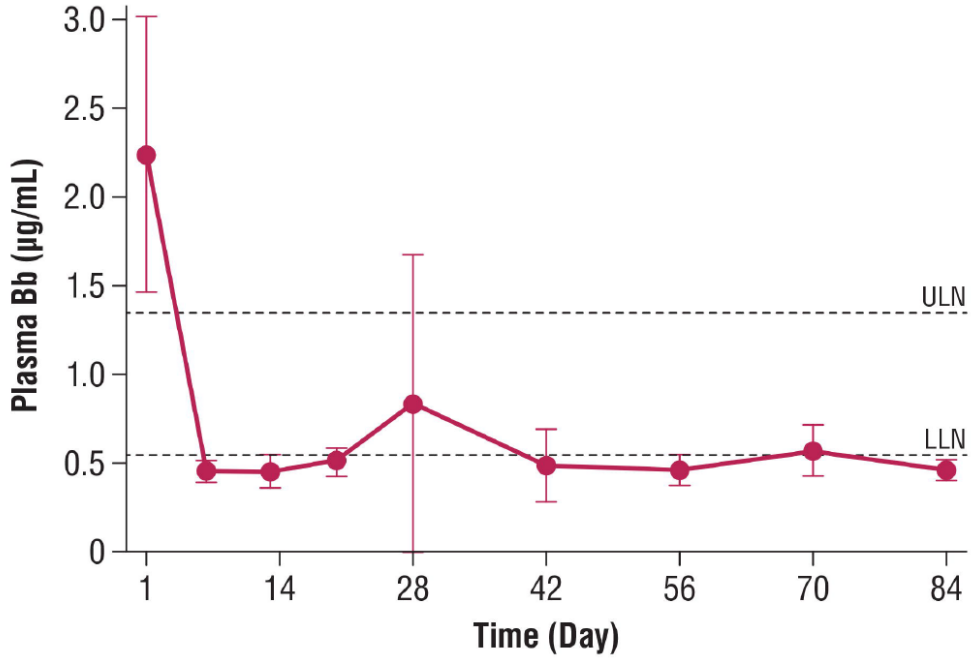


ACH-4471 - Danicopan

Achillion - Alexion

An oral Complement Factor D (CFD) inhibitor thrice daily





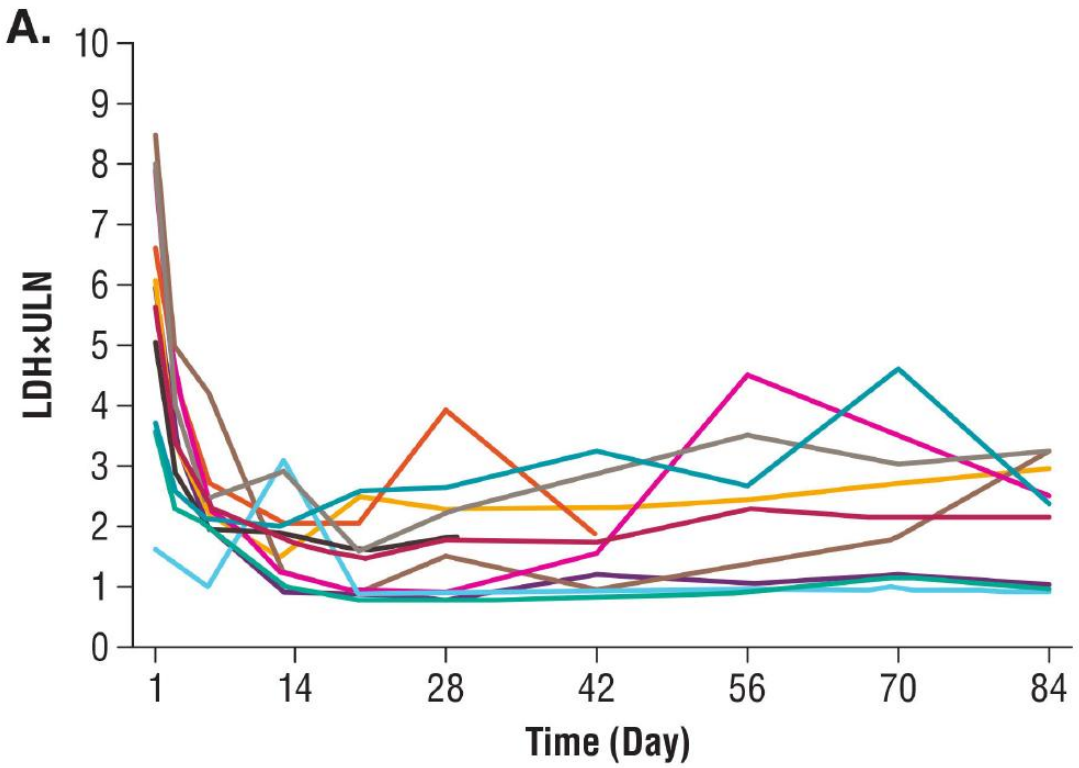
After danicopan, Bb levels were significantly reduced throughout the study

Risitano Haematologica 2021

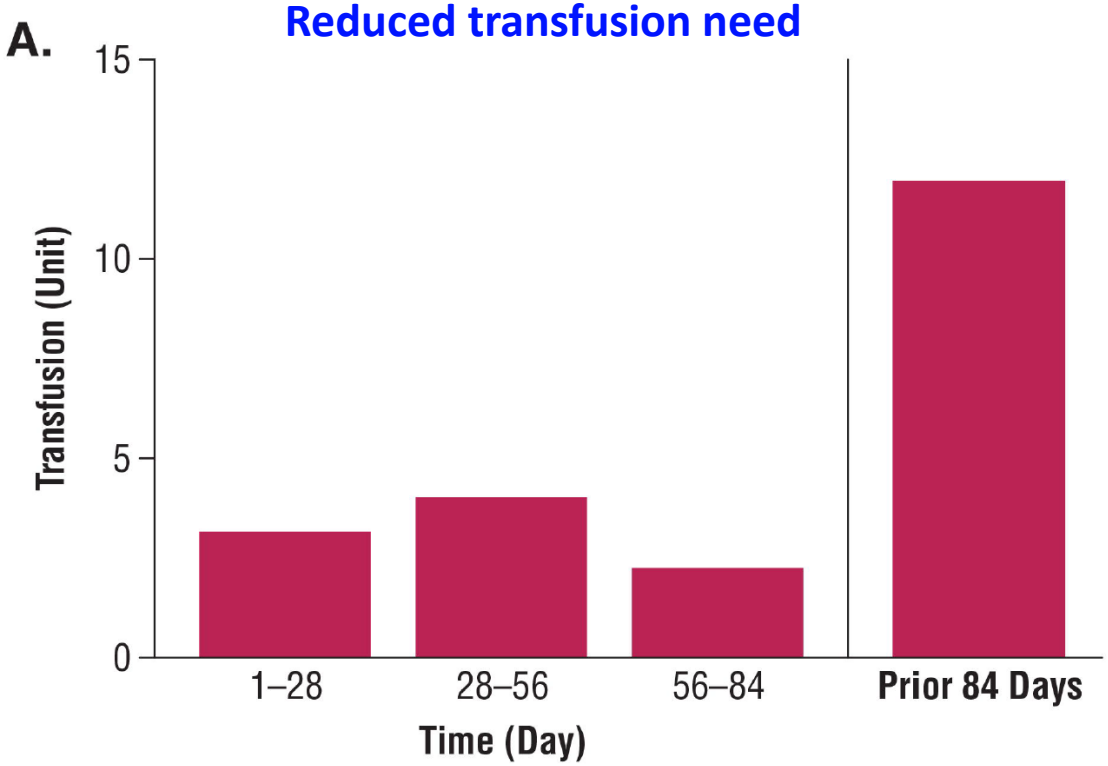
ACH-4471 - Danicopan

Achillion - Alexion

10 untreated hemolytic PNH patients



Reduced transfusion need



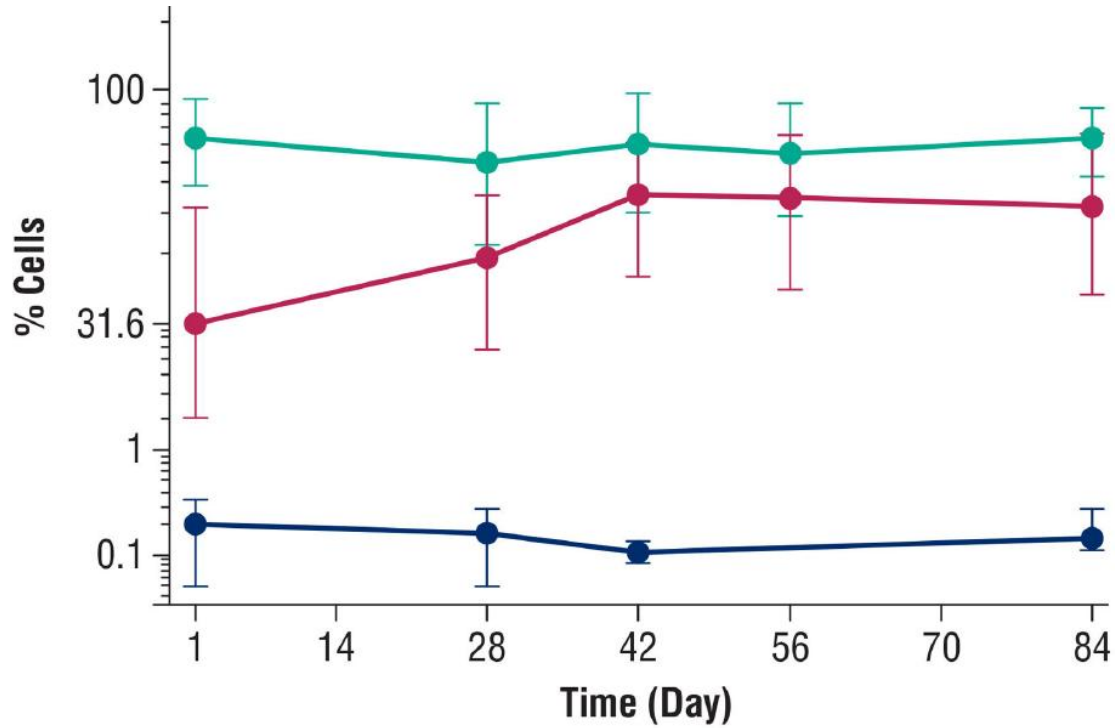
Change in LDH from baseline to day 28 was the primary end point. A significant reduction was observed among all 10 patients from a mean value of 5.7+/-1.7 times ULN at baseline to 1.8+/- times ULN at day 28.

Risitano Haematologica 2021

ACH-4471 - Danicopan

Achillion - Alexion

Importantly, C3 fragment deposition on erythrocytes was very low (<0.5% of erythrocytes) throughout treatment



	Day 1	Day 28	Day 42	Day 56	Day 84
N	10	9	7	5	8
Mean (SD)	32 (24.6)	44 (15.6)	60 (20.1)**	59 (21.0)	56 (19.9)**
Range	11, 78	31, 82	39, 89	39, 91	36, 92

GPI-deficient granulocytes
GPI-deficient erythrocytes
C3d positive erythrocytes

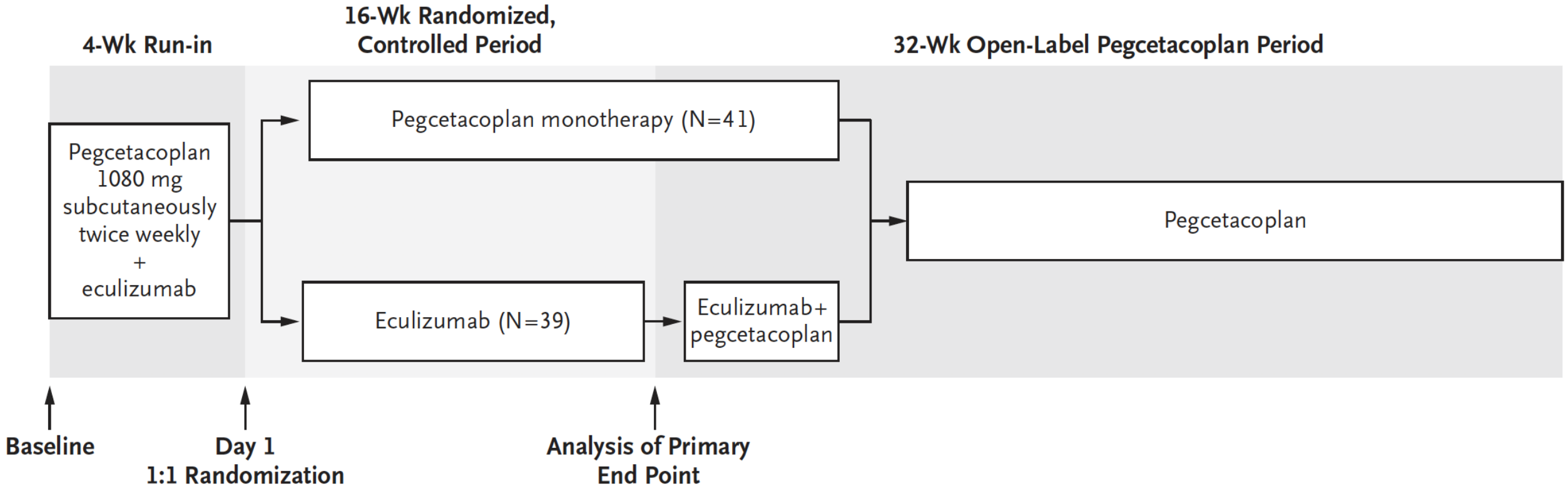
Risitano Haematologica 2020

APL-2 - Pegcetacoplan

SOBI

Targeted C3 inhibitor, consisting of peptides conjugated to a linear polyethylene glycol (PEG)

Subcutaneous administration

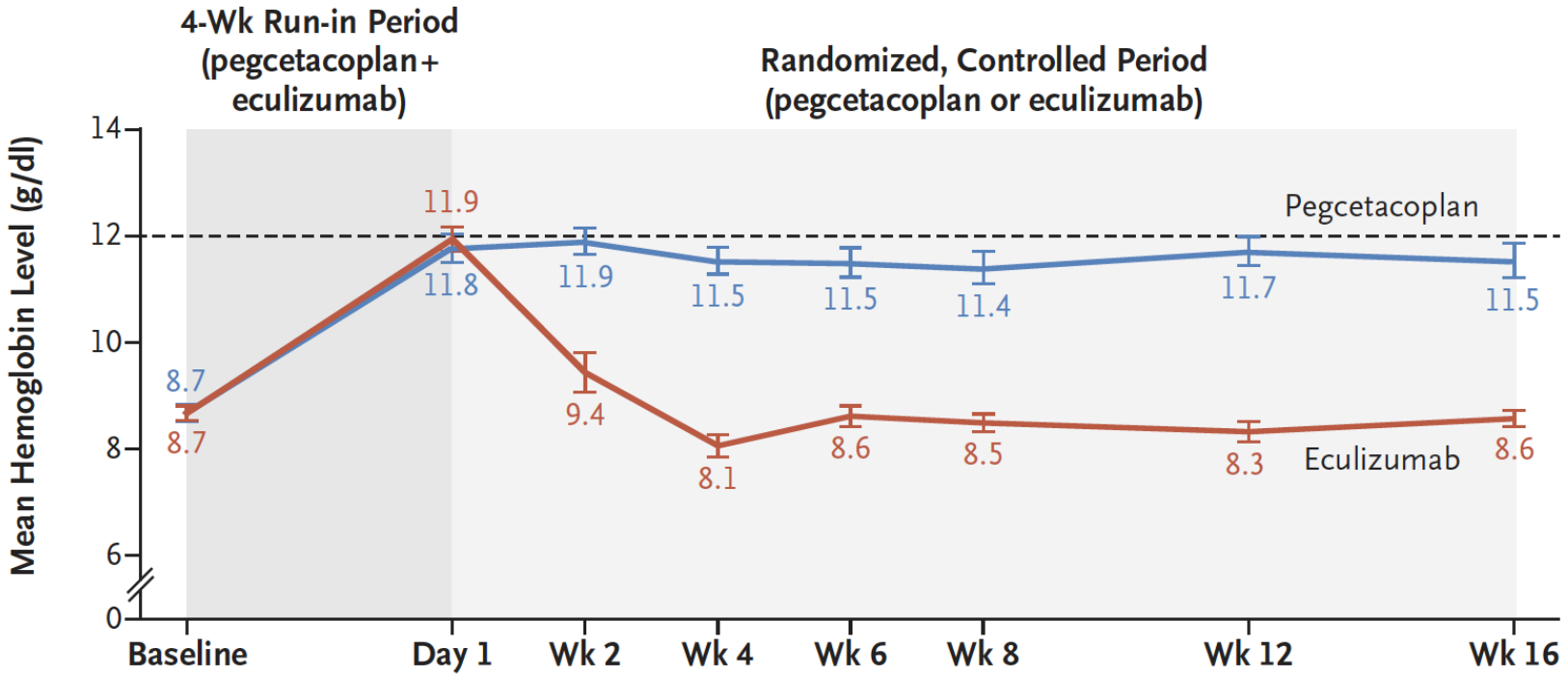


Hillmen NEJM 2021

APL-2 - Pegcetacoplan

SOBI

Pegcetacoplan was superior to eculizumab with respect to the change in hemoglobin level from baseline to week 16, with an adjusted mean difference of 3.84 g/dL (p<0.001).



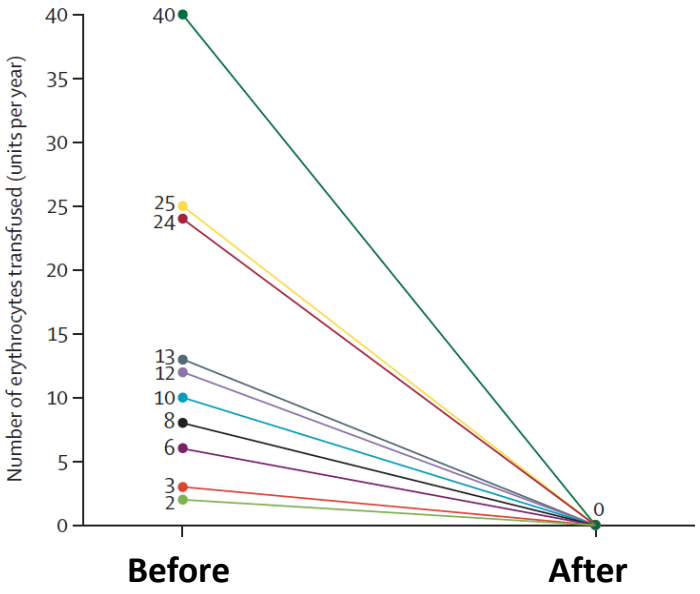
No. with Available Data								
Pegcetacoplan	41	40	40	40	39	37	38	37
Eculizumab	39	37	38	39	36	39	39	38

Hillmen NEJM 2021

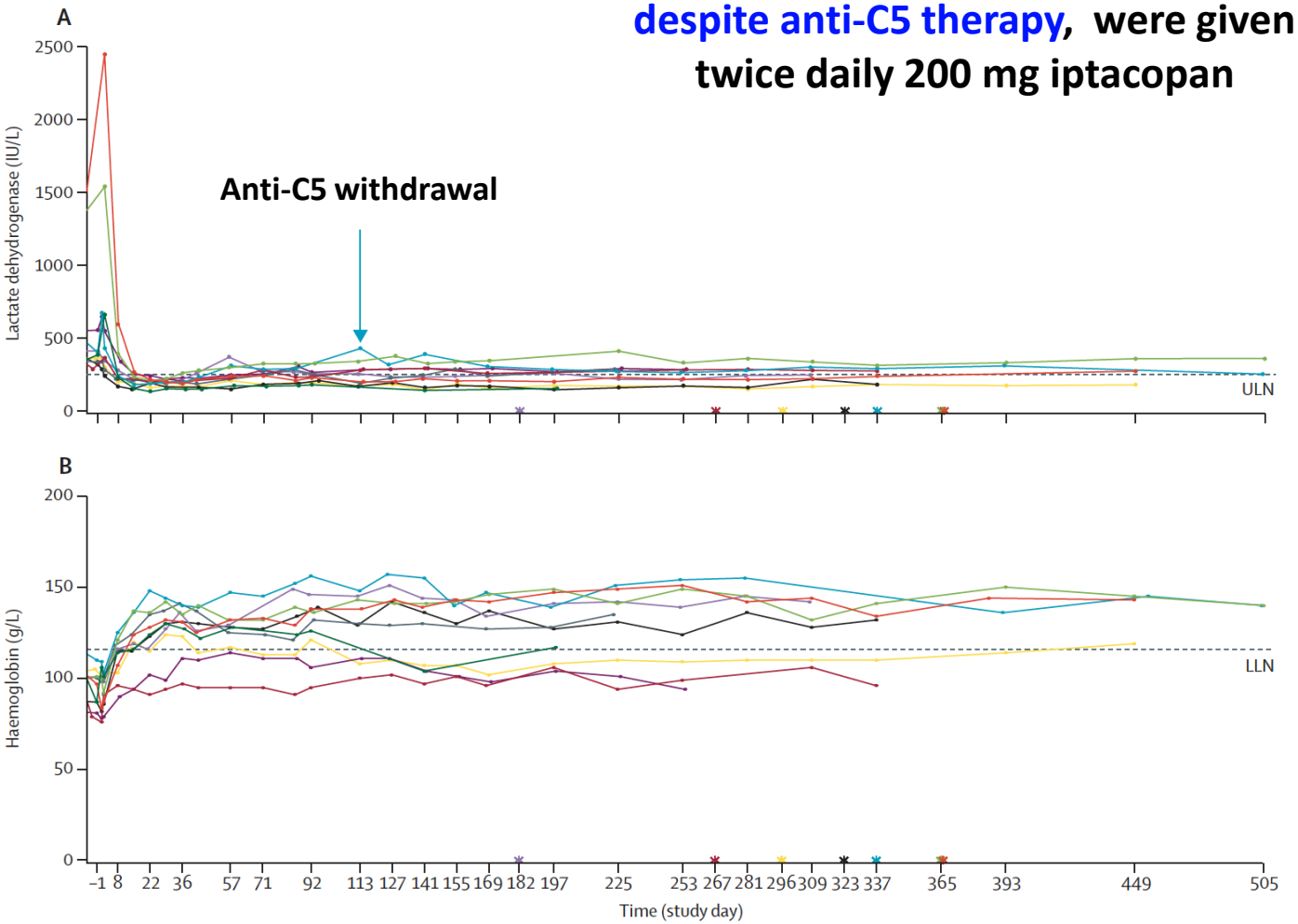
LNP023 - iptacopan

Novartis

An oral Complement Factor B (CFB) inhibitor twice daily



10 PNH patients, with active hemolysis despite anti-C5 therapy, were given twice daily 200 mg iptacopan



Risitano Lancet Hematol 2021

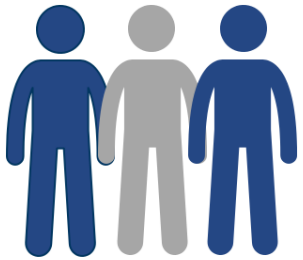
LNP023 - iptacopan

Novartis

C3G

Open-label, 2-cohort, non-randomized, Phase 2 study

To investigate the **efficacy, safety, and PK** of **iptacopan** in **patients** with **C3G with native kidneys** and patients who have undergone **kidney transplantation** and who have demonstrated **C3G recurrence**



Cohort A: Biopsy confirmed C3G patients aged ≥18 years, with native kidneys and reduced serum C3 levels

Cohort B: Adult (≥18 years) patients with C3G recurrence following kidney transplantation

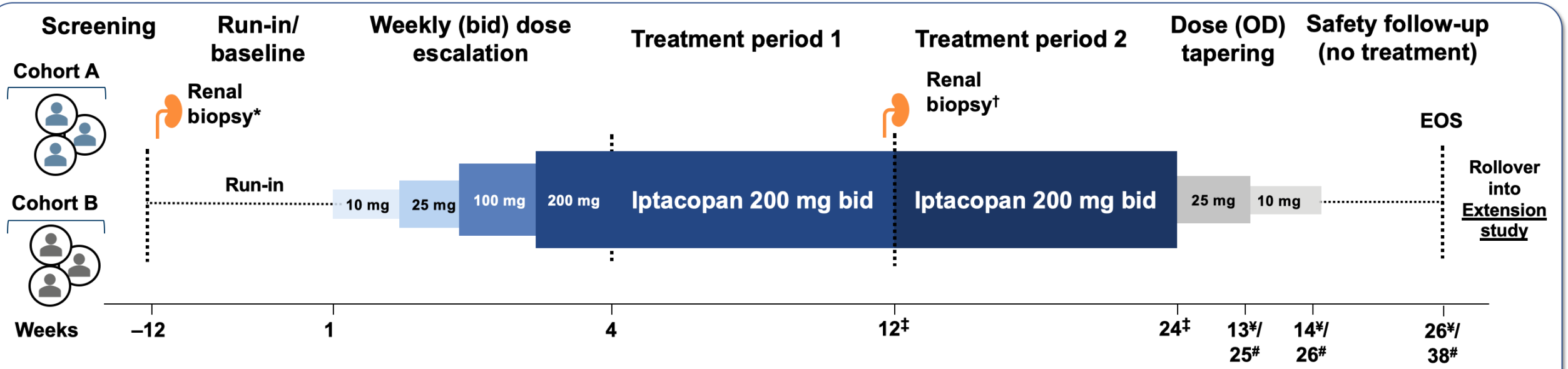
Status:
Completed
IA1: January 2020
IA2: June 2020
Final analysis: June 2021

Wong E. ASN Kidney week 2021

LNP023 - iptacopan

Novartis

C3G



Primary endpoint	• **Cohort A**: Change from baseline in proteinuria (Urine Protein to Creatinine concentration Ratio [UPCR]) at Week 12 • **Cohort B**: Change from baseline in C3 deposit score (based on IF microscopy) at Week 12

Wong E. ASN Kidney week 2021

LNP023 - iptacopan

Novartis

C3G

		Cohort A N=16	Cohort B N=11
Age (years)	Mean (SD)	26.1 (10.57)	34.5 (18.32)
	Median (Range)	**22.0 (18-59)**	**31.0 (18-70)**
Gender - n(%)	Male	10 (63)	8 (73)
Ethicity - n(%)	American Indian or Alaska Native		1 (9)
	Black or African Americans		1 (9)
	White	16 (100)	9 (82)
C3 Deposit Score	n	1	10
	Mean (SD)	12.00	4.15 (3.816)
	Median	12.0	3.0
	Range	12.0 - 12.0	0.0 - 12.0
DDD present – n(%)	No	14 (88)	7 (64)
	Yes	**2 (13)**	**3 (27)**
UPCR 24h (g/mol)	Mean (SD)	454.0 (242.16)	112.3 (178.05)
	Geo-mean	**401.9**	36.2
	CV% geo-mean	53.64	310.78
	Median (Range)	**391 (199-1019)**	24 (9-445)

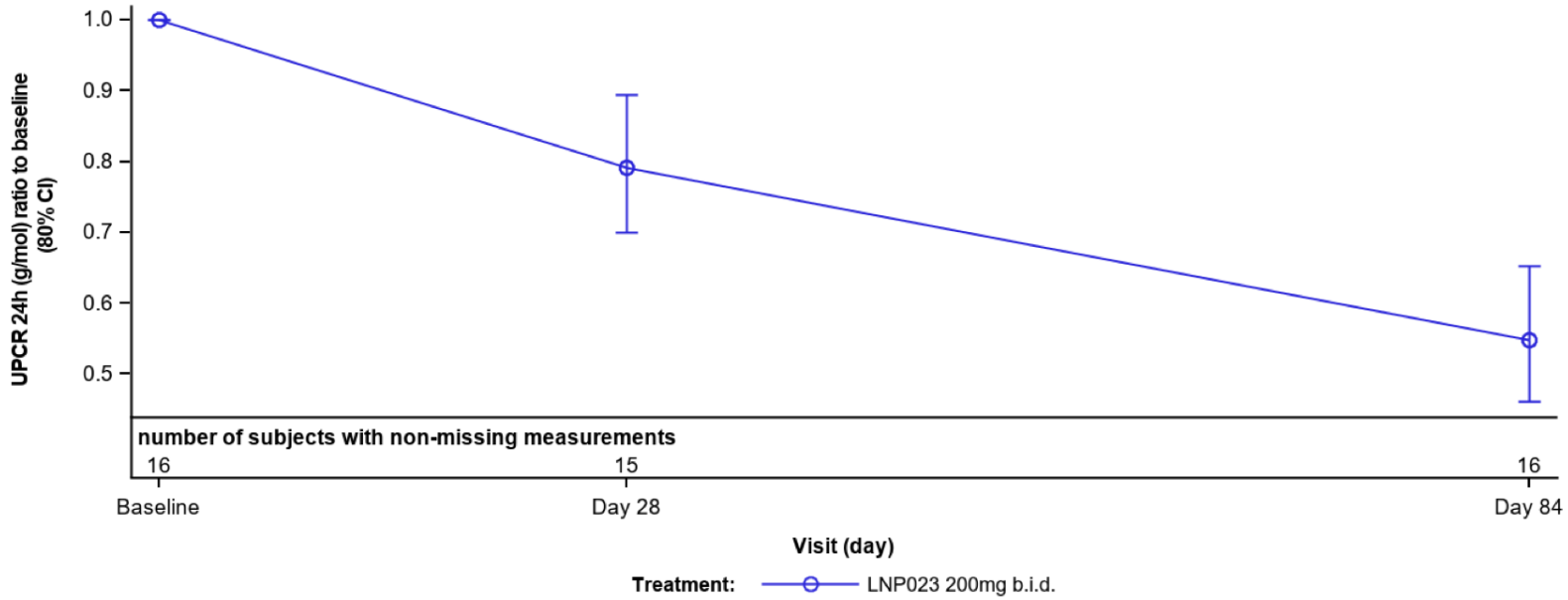
Wong E. ASN Kidney week 2021

LNP023 - iptacopan

Novartis

C3G

Adjusted geometric mean (80% CI) of ratio to baseline for UPCR (24h urine collection)



MMRM of the log transformed ratio to baseline in UPCR

Cohort	Timepoint	N	n	Unadjusted geometric mean ratio to baseline (CV%)	Adjusted geometric mean ratio to baseline (80% CI)*	p-value*
Cohort A	Day 28	16	15[#]	0.80 (34.9)	0.79 (0.70, 0.89)	0.0219
	Day 84	16	16	0.55 (54.4)	0.55 (0.46, 0.65)	**0.0003**

Cohort A primary endpoint achieved with 45% reduction in UPCR 24h (g/mol) vs baseline

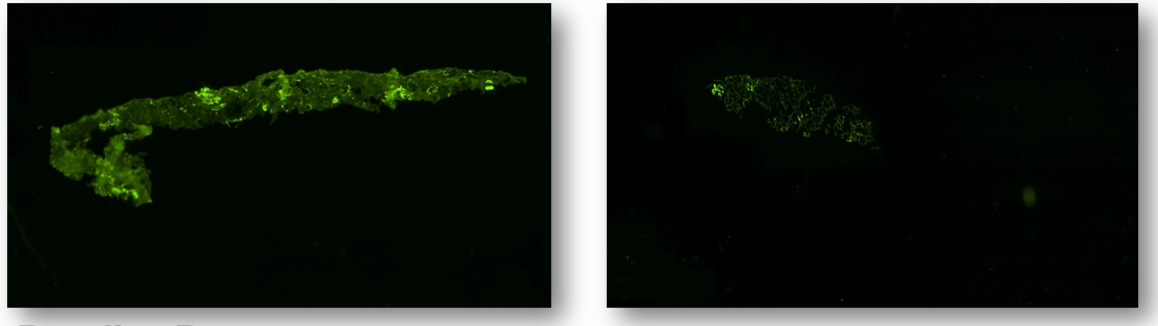
Wong E. ASN Kidney week 2021

LNP023 - iptacopan

Novartis

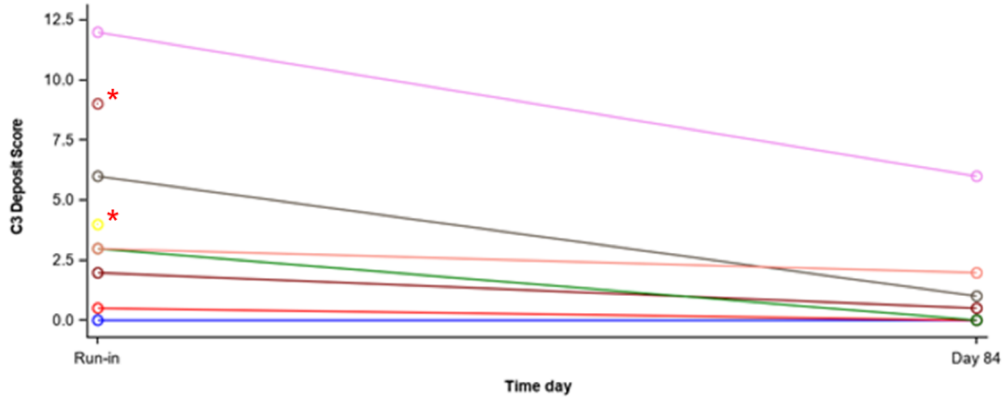
C3G

Kidney Biopsy BL → W12 C3 Deposit Score (ID 4003002)



Baseline Bx | Week 12 Bx

Individual plots for total C3 Deposit Score (Bx)



* subjects with only baseline values

Wilcoxon signed rank test estimate for the median difference of C3 Deposit Score

		Medians		Difference		
N	n	Median Baseline	Median Week 12	Shift Location	80% CI	p-value
7	7	3.00	0.50	-10.5	-2.5 (-3.75, -0.75)	**0.0313**

Cohort B primary endpoint achieved with significant C3 deposit scores reduction vs baseline

Wong E. ASN Kidney week 2021

Outlines

1 - Atypical HUS / TMA

2 - C3G

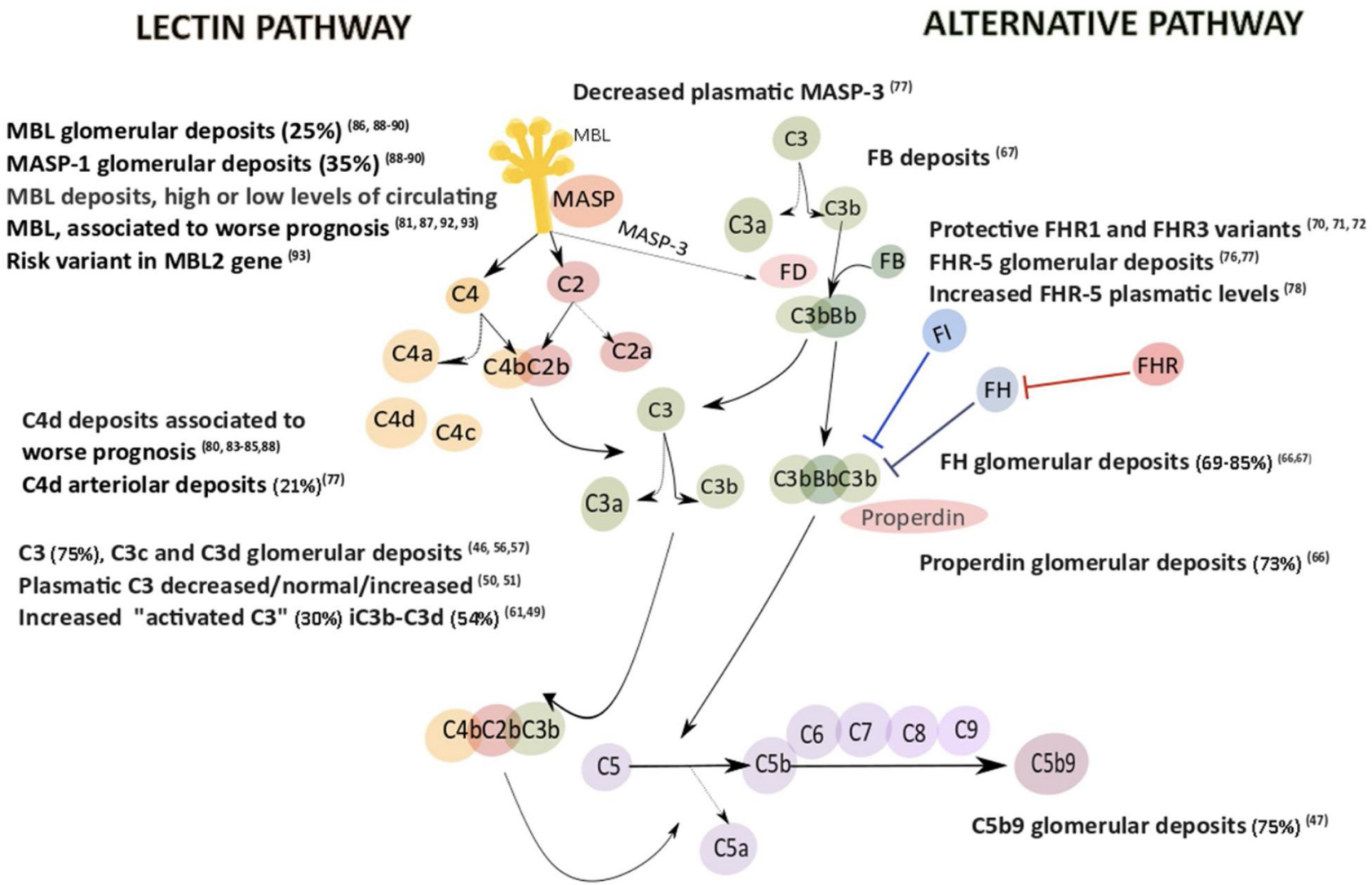
3 - IgAN

4 – Antibody-mediated rejection

5 – Brain death and ischemia reperfusion

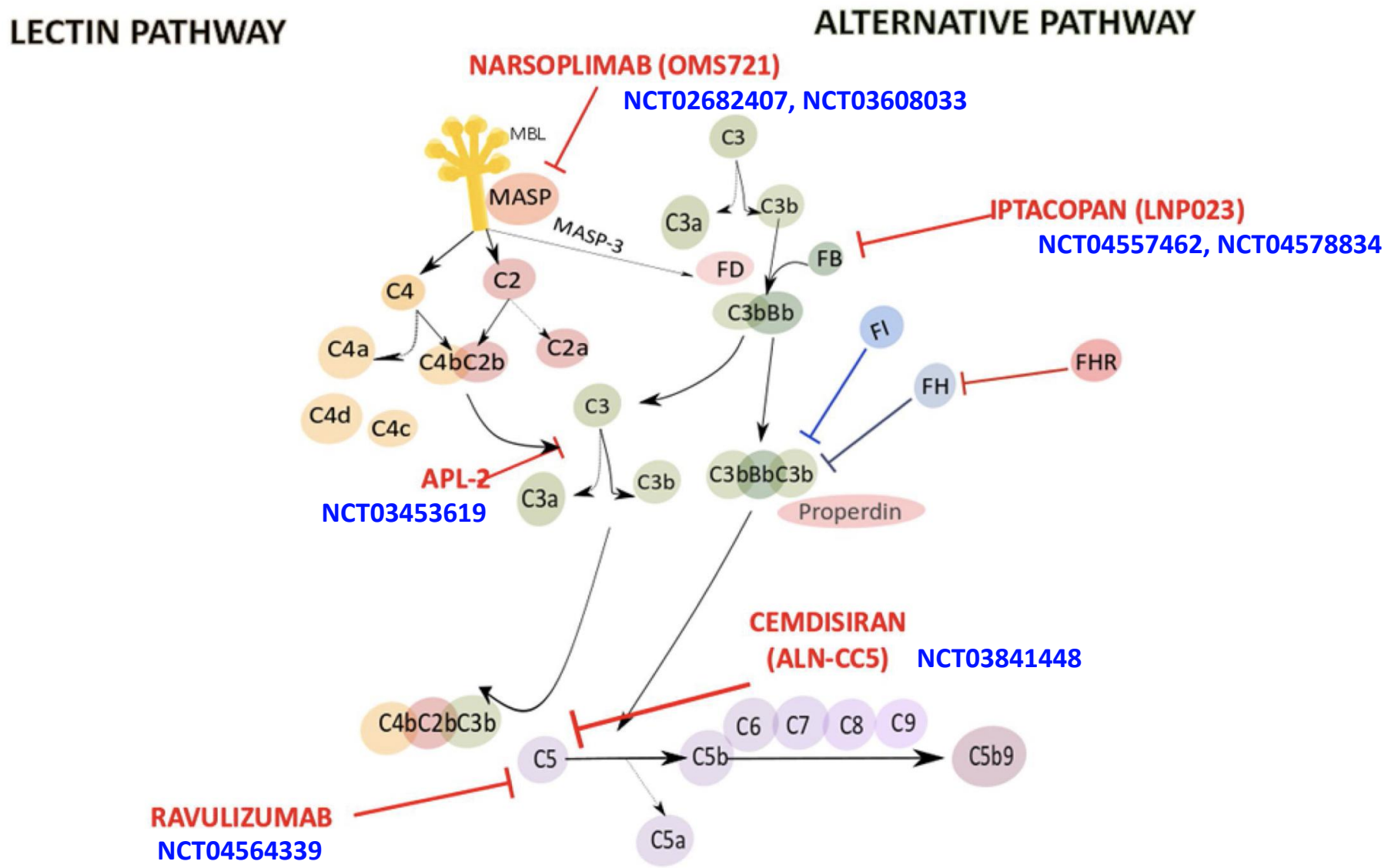
Acknowledgement: Avacopan for ANCA-associated vasculitis is left out in purpose

Lectin and alternative complement pathways are increasingly involved in IgAN



Le Stang Mol Immunol 2021

Ongoing clinical trials – Pending results



Le Stang Mol Immunol 2021

Outlines

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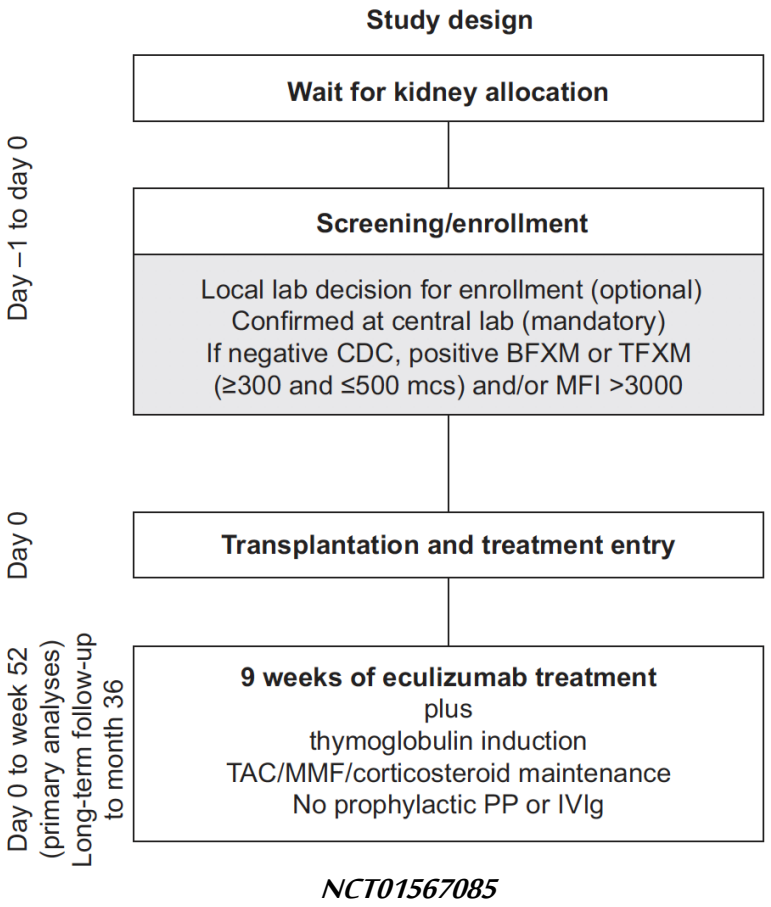
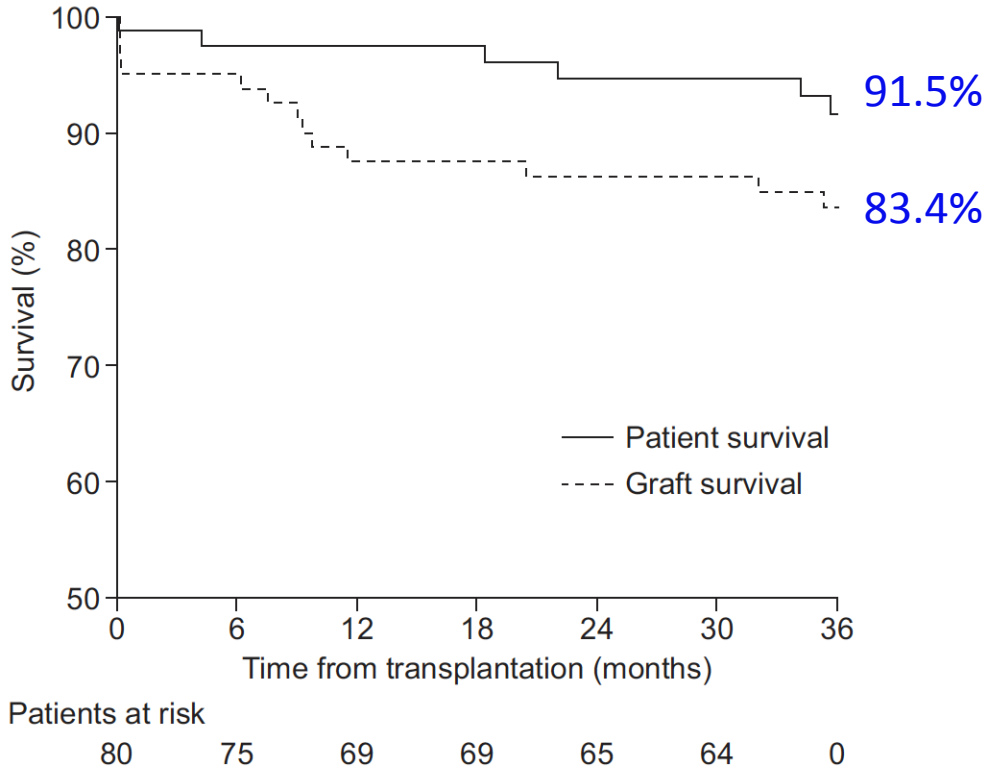
C5 blockade to prevent ABMR in sensitized patients

Prophylaxis

Deceased-donor KTx



Composite primary endpoint: BP AMR, graft loss, death or loss to f/u within 9 weeks



At 9 weeks posttransplant, treatment failure rate was 8.8%, which was significantly lower than the expected failure rate of 40% for the SOC in this population

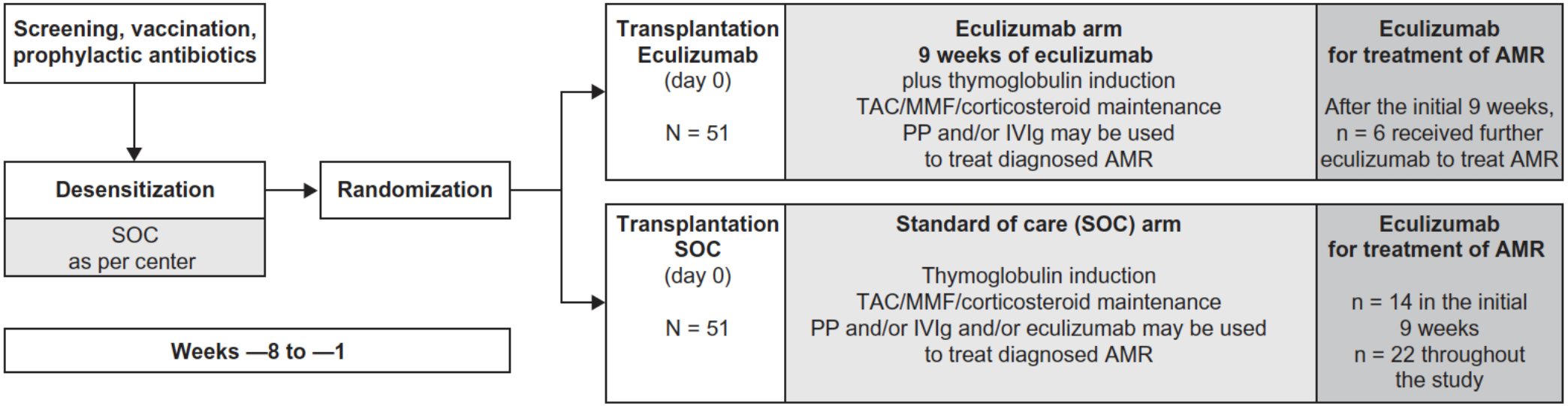
Glotz Am J Transplant 2019

C5 blockade to prevent ABMR in sensitized patients

Prophylaxis

NCT01399593

Composite primary endpoint: BP AMR, graft loss, death or loss to f/u within 9 weeks



Marks Am J Transplant 2019

C5 blockade to prevent ABMR in sensitized patients

Prophylaxis

NCT01399593

	Eculizumab (N = 51) n (%)	SOC (N = 51) n (%)	Difference (exact 95% CI)	*P* value
Composite primary end point				
Treatment failure rate (including grades II and III AMR)	5 (9.8)	7 (13.7)	−3.9% (−23.9, 16.3)	.760
Composite primary end point components				
Acute AMR (grade II or III)	5 (9.8)	5 (9.8)		
Graft loss	0 (0.0)	3 (5.9)		
Death	1 (2.0)	1 (2.0)		
Loss to follow-up	0 (0.0)	2 (3.9)		

No significant difference in treatment failure rate was observed between eculizumab (9.8%) and SOC (13.7%; p=0.76)

Marks Am J Transplant 2019

C5 blockade to prevent ABMR in sensitized patients

Prophylaxis

NCT01567085
NCT01399593

Characteristics	Patients with C1q+ anti-HLA DSAs, *n*=69			Patients with C1q− Anti-HLA DSAs, *n*=47		
	SOC, *n*=32	Eculizumab, *n*=37	*P* Value	SOC, *n*=32	Eculizumab, *n*=15	*P* Value
Clinical parameters, mean (SD)						
eGFR, ml/min per 1.73 m^2	44.8 (15.7)	47.2 (18.1)	0.65	46.2 (15.6)	48.1 (13.8)	0.63
Proteinuria, g/g	0.6 (0.6)	0.3 (0.3)	0.02	0.3 (0.2)	0.3 (0.2)	0.61
Histology (Banff scores), median (IQR)						
g score	2 (1–2)	1 (0–1)	0.001	1 (0–2)	1 (0–2)	0.82
ptc score	2 (1–2)	0 (0–1)	<0.001	1 (0–1)	0 (0–1)	0.85
v score	0 (0–0)	0 (0–0)	0.30	0 (0–0)	0 (0–0)	0.42
i score	1 (0–1)	0 (0–0)	<0.001	0 (0–0)	0 (0–1)	0.88
t score	1 (0–2)	0 (0–0)	<0.001	0 (0–1)	0 (0–1)	0.73
cg score	0 (0–0)	0 (0–0)	0.12	0 (0–0)	0 (0–0)	0.51
C4d score	2 (1–2)	3 (0–3)	0.23	0 (0–1)	0 (0–2)	0.64
Gene expression level (log2 OD), mean (SD)						
CXCL11	8.9 (1.8)	4.9 (2.3)	<0.001	4.3 (1.5)	4.1 (1.0)	0.99
CCL4	9.7 (1.8)	6.8 (2.2)	<0.001	6.5 (1.6)	6.1 (1.5)	0.52
MS4A6A	9.3 (2.1)	6.8 (2.6)	<0.001	7.0 (2.4)	6.7 (2.5)	0.78
MS4A7	8.1 (2.1)	5.7 (2.6)	<0.001	5.2 (2.6)	5.4 (2.5)	0.79
FCGR3A	9.2 (1.8)	6.3 (2.2)	<0.001	6.0 (1.8)	5.7 (1.8)	0.66

Compared with SOC, eculizumab specifically abrogated histomolecular rejection phenotype and associated with a decreased 3-month rejection incidence rate in patients with complement-activating DSAs but not in those with noncomplement-activating DSAs

Lefaucheur JASN 2018

C1-INH as first-line therapy in ABMR

Cinryze (Shire)

First-line

NCT02547220

Efficacy and Safety of C1INH for the treatment of acute AMR in KTx

Interventional Randomized double blind study that aims to evaluate the efficacy and safety of C1 inhibition for the treatment of acute AMR (phase 3).

Primary outcome: proportion of subjects with new or worsening transplant glomerulopathy within 6 months post-treatment

56 patients in each arm (C1INH vs placebo)

7 doses of Cinryze vs placebo over 13 days

This study was prematurely terminated at Month 36 due to futility issue.

Outlines

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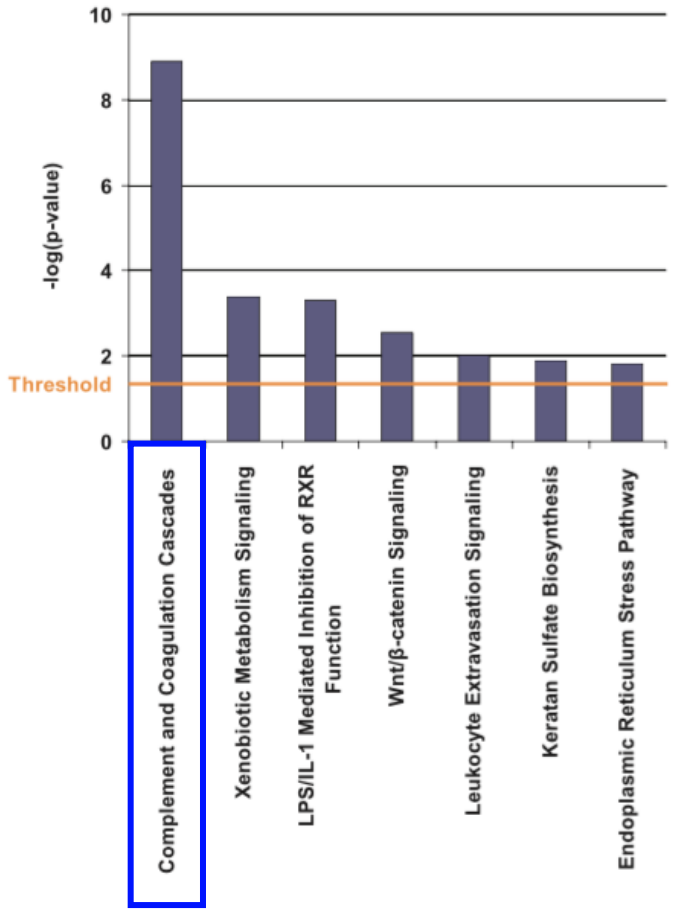
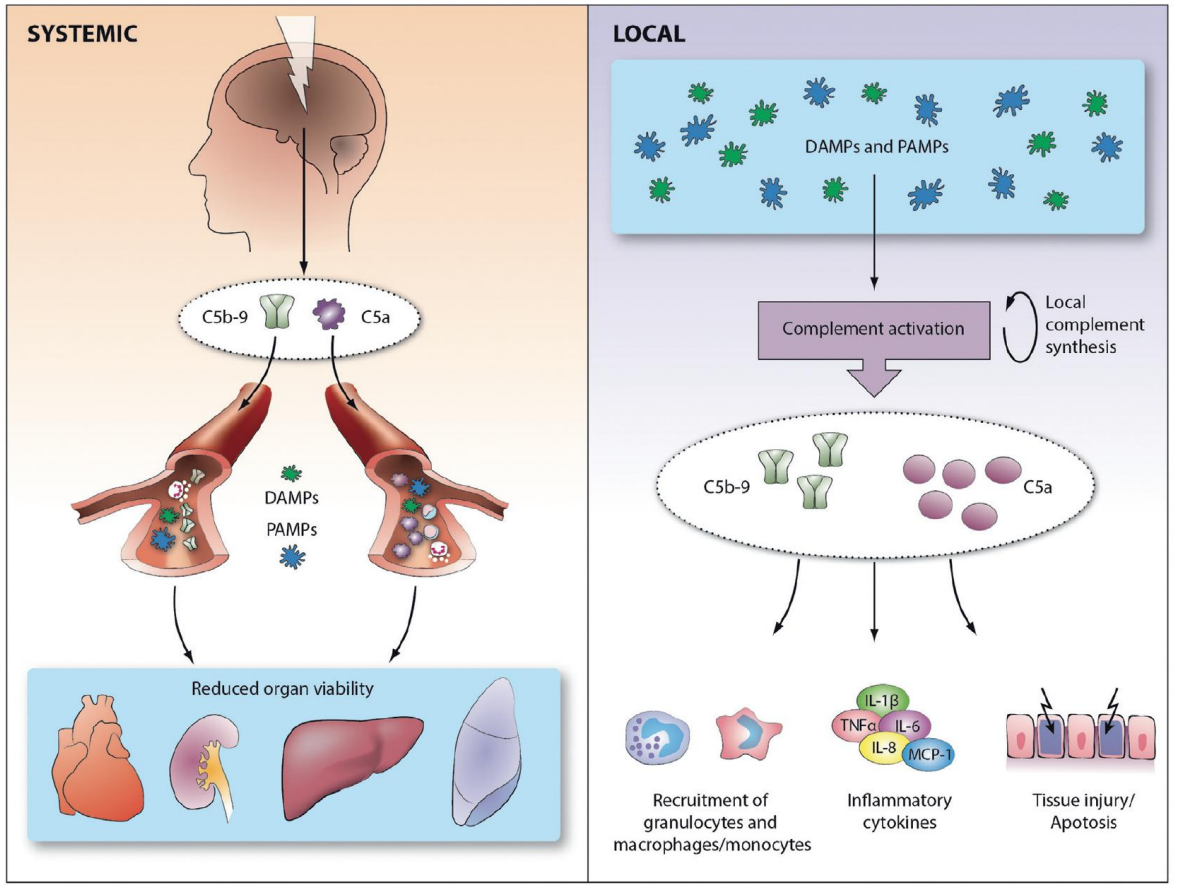
5 – Brain death and ischemia reperfusion

Acknowledgement: Avacopan for ANCA-associated vasculitis is left out in purpose

Brain death and IRI through the molecular microscope

The transcripts the most significantly increased in Deceased vs Living donors include those from the complement and coagulation cascades

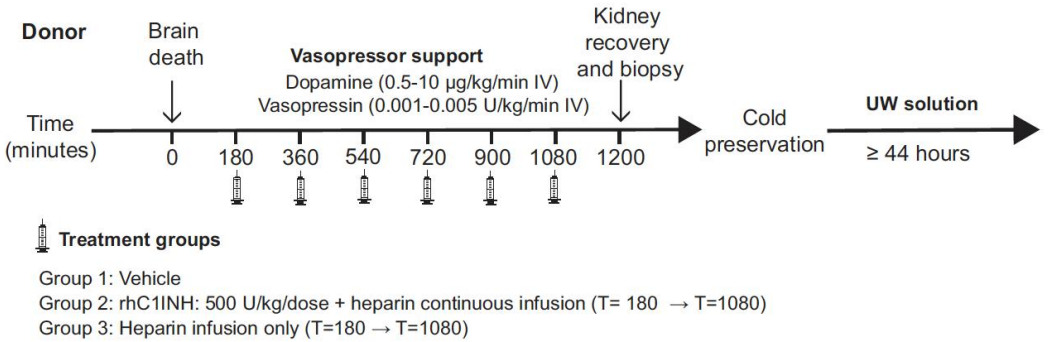




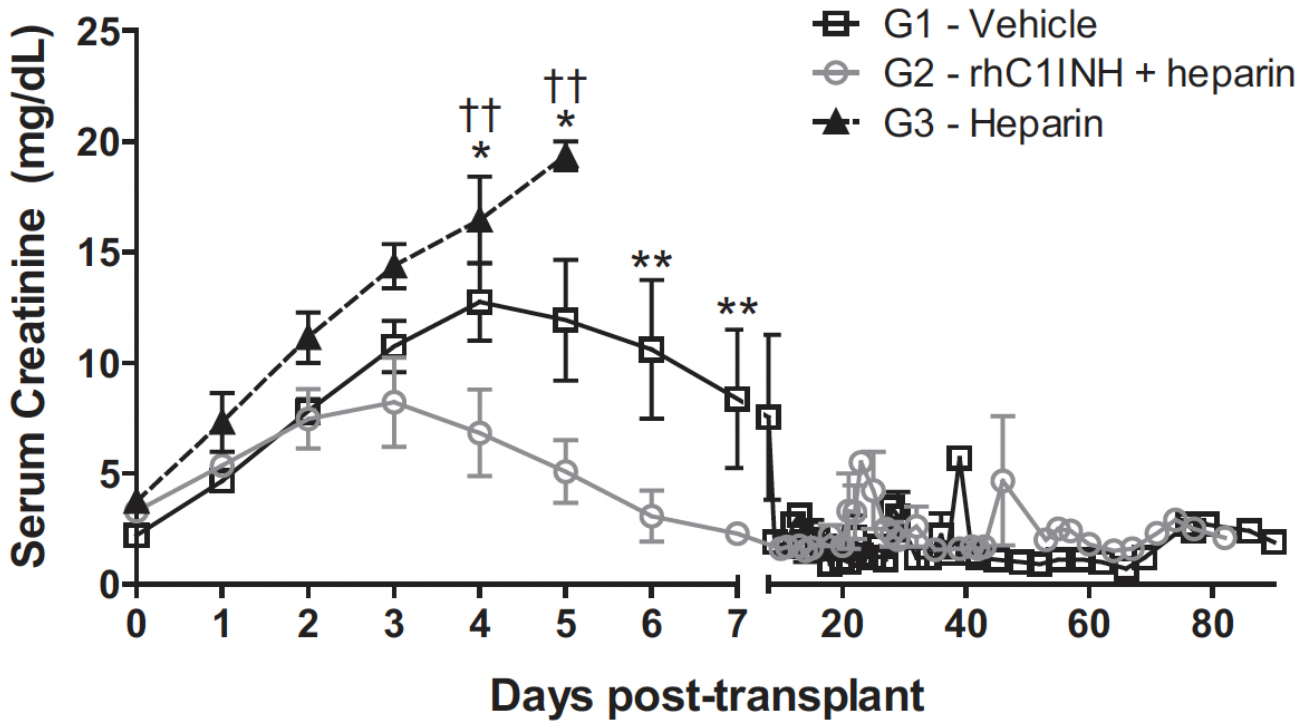
The systemic inflammation initiated by BD induces a more local organ inflammation, priming the organs for IRI, and leading to an influx of inflammatory cells.

Naesens J Am Soc Nephrol 2009

Complement blockade after brain death prevents DGF



rhC1-INH (500 U/kg/dose)



Danobeita Am J Transplant 2020

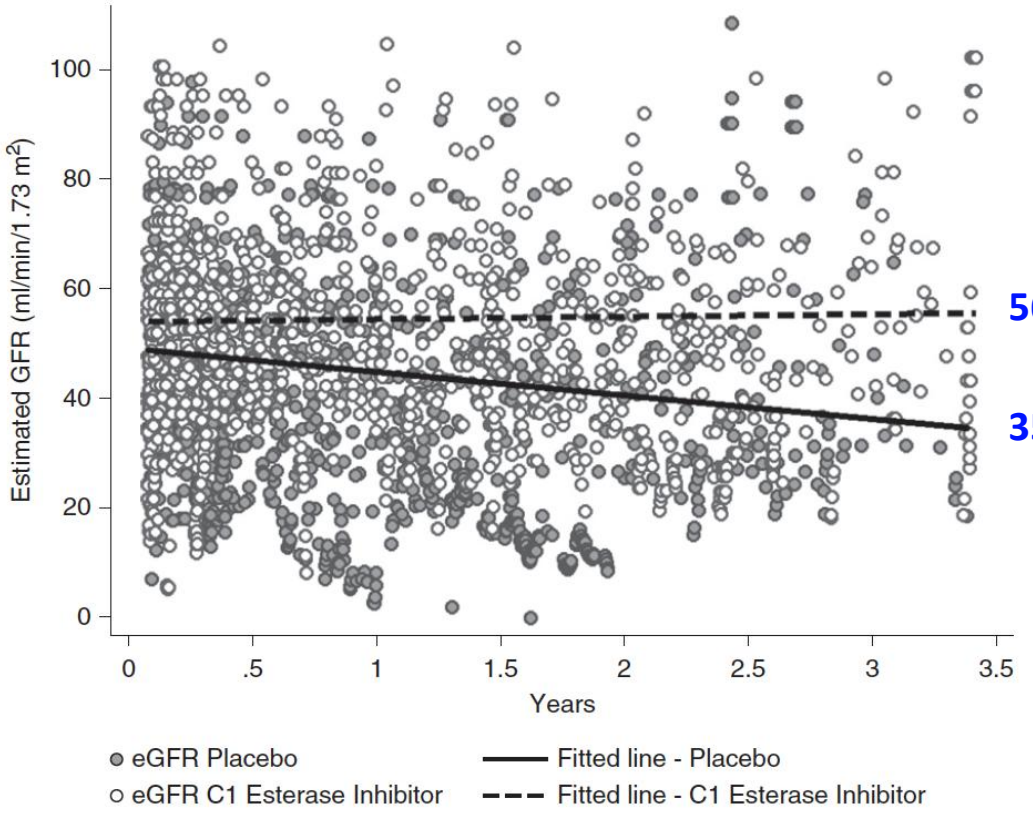
C1-INH in Expanded Criteria Donors

NCT02134314

Primary outcomes: Number of patients with DGF and SGF

Randomization: 35 patients in each arm (C1INH vs placebo)

C1INH (50 U/kg) administered pre-transplant and 24 hours post-transplant.



56 ml/mn/1.73 m²

35 ml/mn/1.73 m²

p=0.03

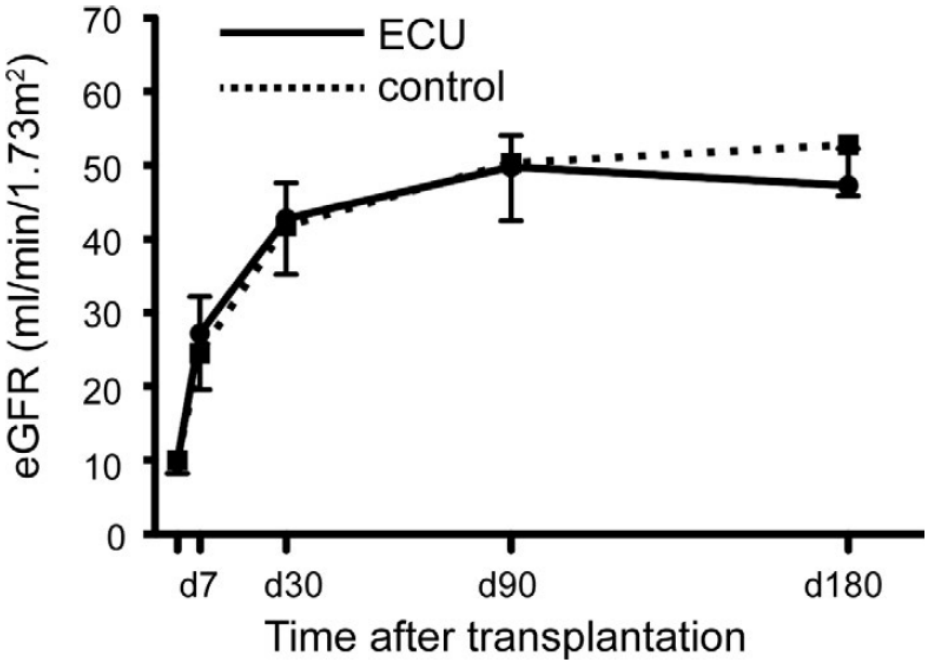
Huang CJASN 2020

C5 blockade in Expanded Criteria Donors

NCT01403389
NCT01919346

Pilot phase 2 (n=8+21)

One pretransplant dose (+/- one early post-transplant dose)



Peri-transplant C5 blockade failed to improve the rate of Delayed Graft Function

Phase 3 (n=288/400)

PROTECT Study (NCT02145182)

Study completed after 288 enrollments. Because the study failed to demonstrate a treatment effect (at the intermediate analysis) and the program subsequently lost funding, all collected data could not be analyzed (ClinicalTrials.gov)

Schröppel Am J Transplant 2020

In summary

- **To be as efficient as eculizumab**
  - **- aHUS: Likely (for other C5 blockers) ; TBD for MASP, C3, CFB and CFD blockers**
  - **- HSCT-TMA: MASP inhibitor might be even more efficient than C5 blocker**
  - **- C3G: C3 / CFB / CFD inhibitors should be more efficient than C5 blocker**
  - **- IgAN: lectin and alternative pathway inhibitors might be more efficient than C5 blocker**
- **Less constraints in terms of the route of administration and drug scheduling**
  - **- Subcutaneous,**
  - **- Long-acting Ab**
- **Similar or greater safety profile**
  - **- Increased susceptibility to meningoccal infection should be shared by all C5 blockers**
  - **- C3 blockade might be associated with a broader immune deficiency ?**
  - **- Single pathway inhibitor (either CP, LP or AP) should be associated with a narrower ID**
- **Cheaper**
  - **- Pending question**

In summary

There is no « One-size-fits-all » complement inhibitor