University of Iowa
Stead Family
Children's Hospital

# C3 Glomerulopathy

# Next Generation of Treatment

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October 17, 2020

# Disclosures

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The following includes a list of current (within the last 24 months) affiliations:

| Affiliation / Financial Interest | Organization |
|---|---|
| Associate Director | Molecular Otolaryngology and Renal Research Laboratory |
| NIH | 1R01DK110023-01A1 |
| Site Investigator | ChemoCentryx |
| Site Investigator | Achillion Pharmaceuticals |
| Site Investigator | Alexion Pharmaceuticals |
| Site Investigator, Research Funding | Novartis |
| Site Investigator | Retrophin |
| Advisory Board | BioCryst |

My conflicts are managed by a University of Iowa mandatory conflict plan.
Both prior and current relationships are on record at the University of Iowa's Conflict in Research Office:
https://coi.research.uiowa.edu/

# Objectives

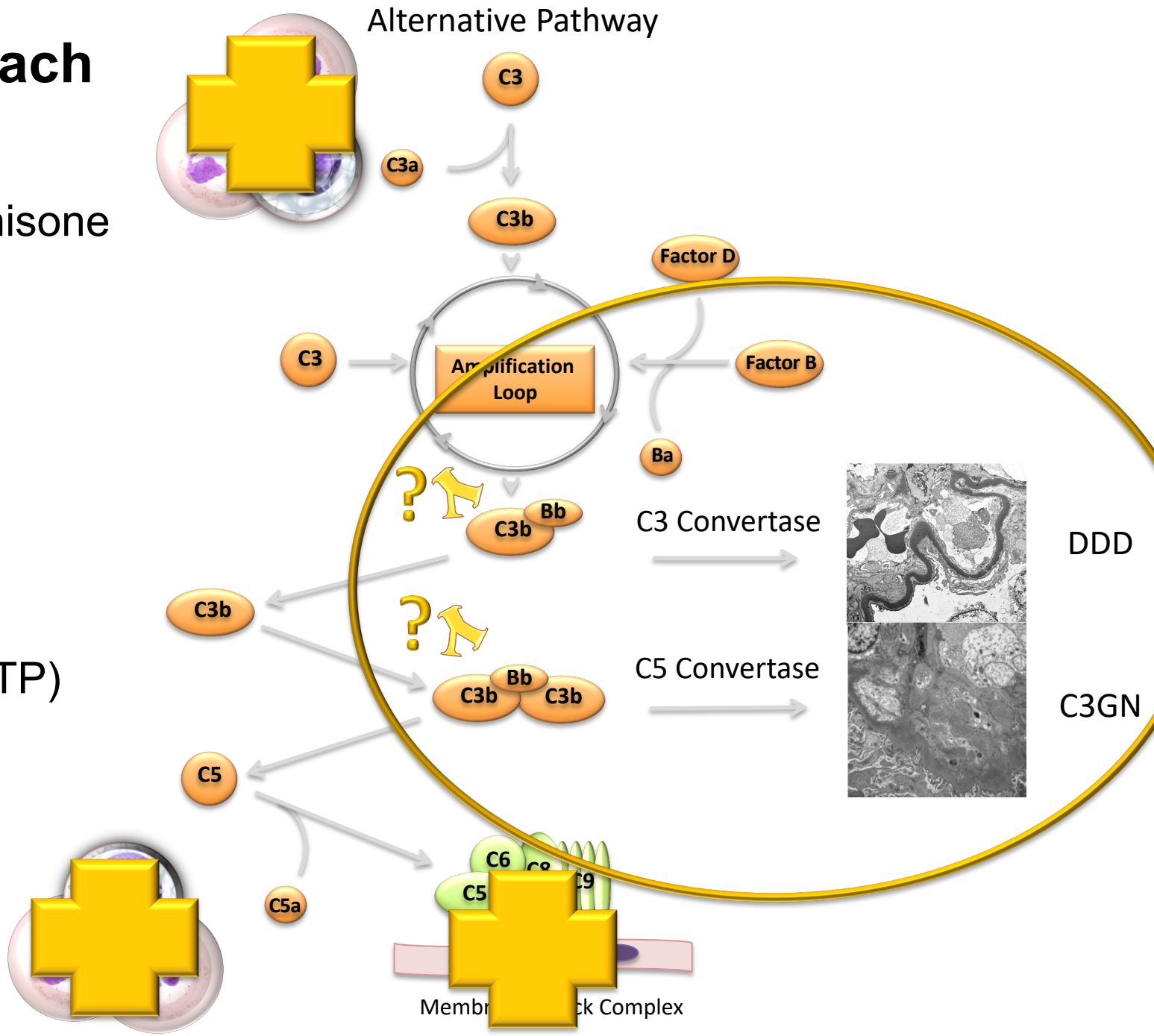


- Staying up to date on C3 Glomerulopathy Clinical Trials
- Brief review of trial design
- Therapeutic targets of agents in the pipeline

# Current Therapeutic Approach

1. Mycophenolate mofetil and prednisone

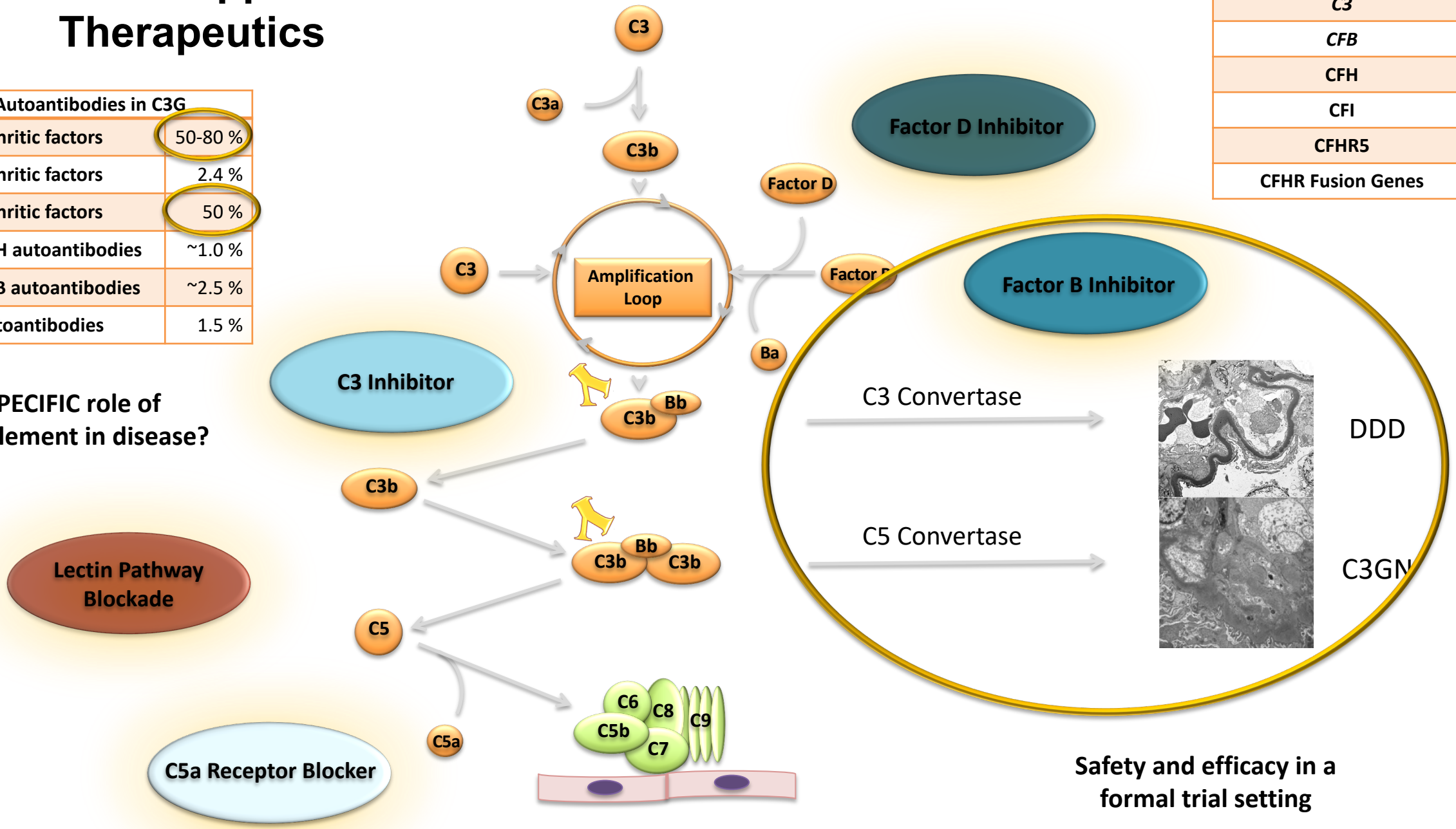
2. Terminal Complement Pathway (TP) Blockade



# Theoretical Approach to Therapeutics

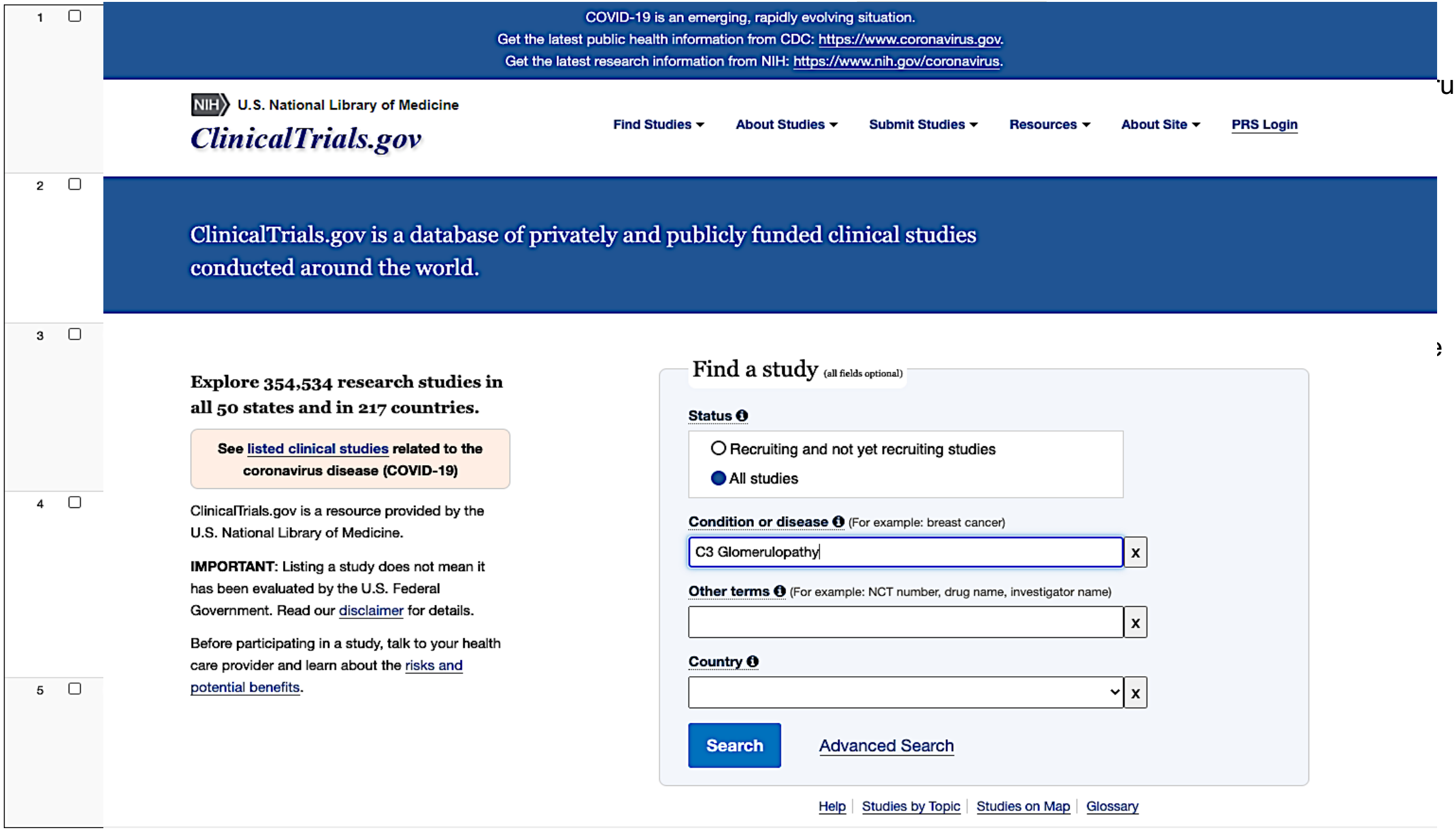
| Autoantibodies in C3G | |
|---|---|
| C3 nephritic factors | 50-80 % |
| C4 nephritic factors | 2.4 % |
| C5 nephritic factors | 50 % |
| Factor H autoantibodies | ~1.0 % |
| Factor B autoantibodies | ~2.5 % |
| C3b autoantibodies | 1.5 % |

**SPECIFIC role of complement in disease?**




| Genetic Drivers ~25% |
|---|
| *C3* |
| *CFB* |
| CFH |
| CFI |
| CFHR5 |
| CFHR Fusion Genes |

**Safety and efficacy in a formal trial setting**




https://clinicaltrials.gov/

# Omeros

Lectin Pathway Blockade

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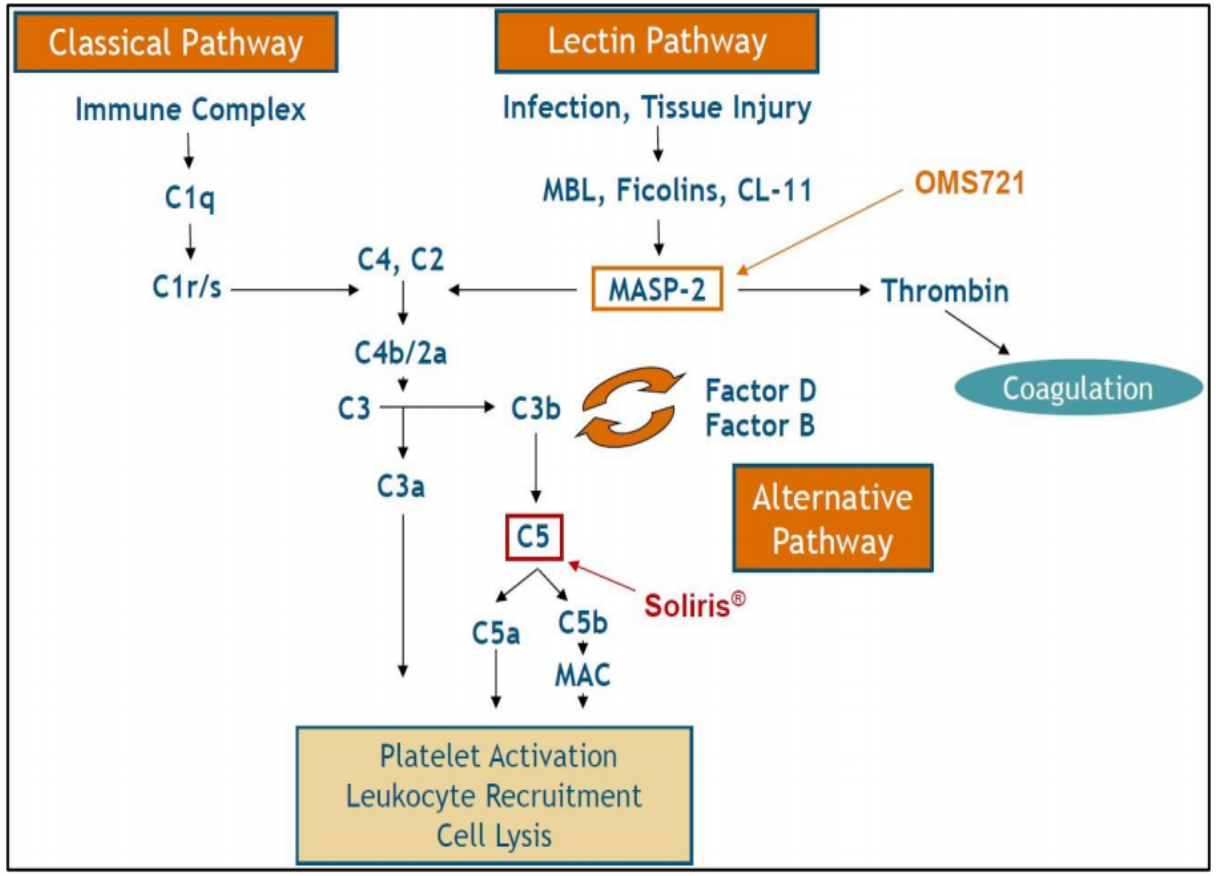
- OMS721 – narsoplimab
- Phase 2
  - Evaluate Safety and Effect on Proteinuria
    - IgA Nephropathy
    - Lupus Nephritis
    - Membranous Nephropathy
    - C3 Glomerulopathy



# Achillion

Factor D Inhibitor

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- ACH-0144471 – Phase 2

BIOPHARMA

## Alexion drops kidney disease program for drug that was part of $930M Achillion buyout last year

The company said in its 2Q earnings that it would halt development of ALXN2040 for C3 glomerulopathy, or C3G, citing the drug's lack of potency. However, it may develop a second, more potent drug from the Achillion acquisition, ALXN2050, in the same disease.

By ALARIC DEARMENT

Post a comment / Jul 30, 2020 at 12:36 PM

# Chemocentryx

C5a Receptor Blocker

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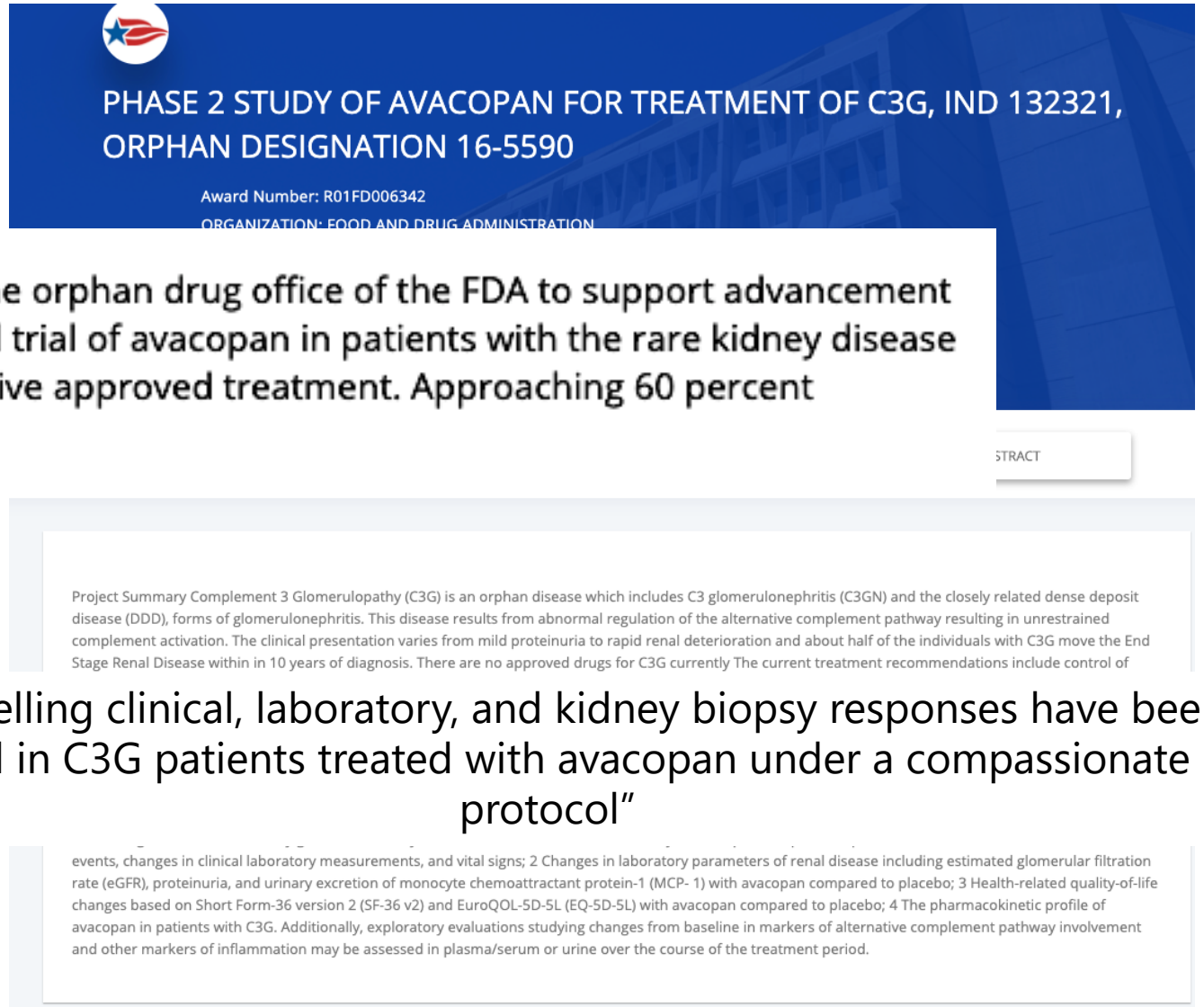
- CCX (Avacopan)



PHASE 2 STUDY OF AVACOPAN FOR TREATMENT OF C3G, IND 132321, ORPHAN DESIGNATION 16-5590

Award Number: R01FD006342

ORGANIZATION: FOOD AND DRUG ADMINISTRATION

- Awarded a two-year $1 million grant from the orphan drug office of the FDA to support advancement in the Company's ACCOLADE Phase II clinical trial of avacopan in patients with the rare kidney disease C3 Glomerulopathy, a disease with no effective approved treatment. Approaching 60 percent enrollment in the ACCOLADE trial.

STRACT

Project Summary Complement 3 Glomerulopathy (C3G) is an orphan disease which includes C3 glomerulonephritis (C3GN) and the closely related dense deposit disease (DDD), forms of glomerulonephritis. This disease results from abnormal regulation of the alternative complement pathway resulting in unrestrained complement activation. The clinical presentation varies from mild proteinuria to rapid renal deterioration and about half of the individuals with C3G move the End Stage Renal Disease within in 10 years of diagnosis. There are no approved drugs for C3G currently The current treatment recommendations include control of

events, changes in clinical laboratory measurements, and vital signs; 2 Changes in laboratory parameters of renal disease including estimated glomerular filtration rate (eGFR), proteinuria, and urinary excretion of monocyte chemoattractant protein-1 (MCP- 1) with avacopan compared to placebo; 3 Health-related quality-of-life changes based on Short Form-36 version 2 (SF-36 v2) and EuroQOL-5D-5L (EQ-5D-5L) with avacopan compared to placebo; 4 The pharmacokinetic profile of avacopan in patients with C3G. Additionally, exploratory evaluations studying changes from baseline in markers of alternative complement pathway involvement and other markers of inflammation may be assessed in plasma/serum or urine over the course of the treatment period.

**Preliminary data for Phase 2 Pending**

"compelling clinical, laboratory, and kidney biopsy responses have been observed in C3G patients treated with avacopan under a compassionate use protocol"

# LNP023

Factor B Inhibitor

Data not for public distribution

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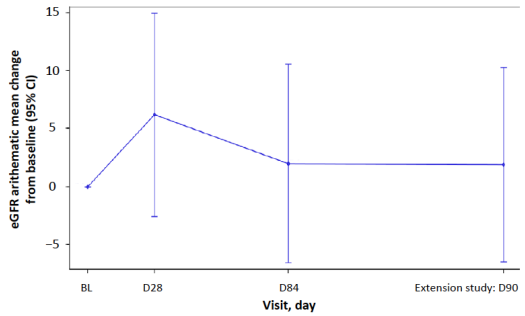
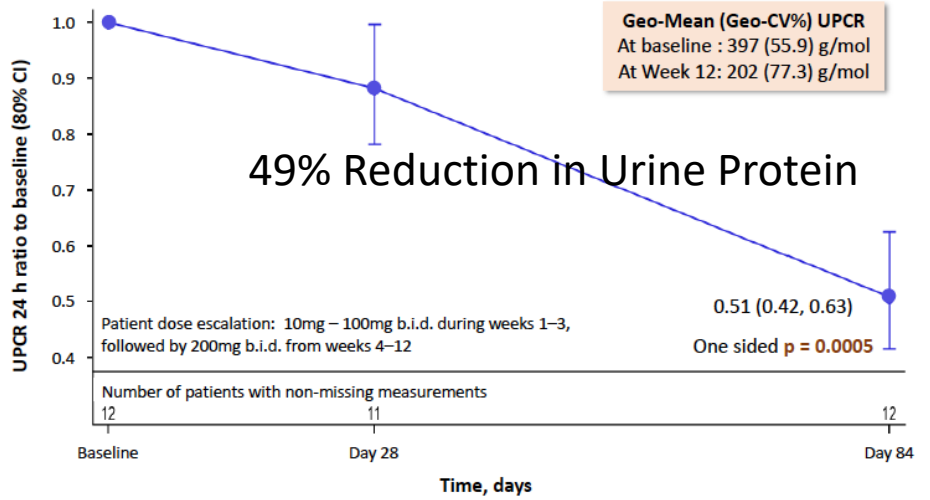
## Complement Factor B Inhibitor (P2)

| | | 12 patients (11 C3GN, 1 DDD) |
|---|---|---|
| **Age (years)** | Mean (SD) | 26.1 (12.1) |
| | Range | 18 – 59 |
| **Gender (N)** | Male / Female | 10 / 2 |
| **Race (N)** | Caucasian / Other | 12 / 0 |
| **Weight (kg)** | Mean (SD) | 68.2 (9.0) |
| **Body Mass Index (kg/m²)** | Mean (SD) | 22.2 (2.7) |
| **Estimated GFR (mL/min/1.73m²)** | Geo-mean (CV%) | 57.9 (65.46) |
| | Median | 56.2 |
| | Range | 28 – 134 |
| **Urine protein:creatinine ratio (g/mol)** | Geo-mean (CV%) | 397.4 (56.0) |
| | Median | 359 |
| | Range | 221-1019 |

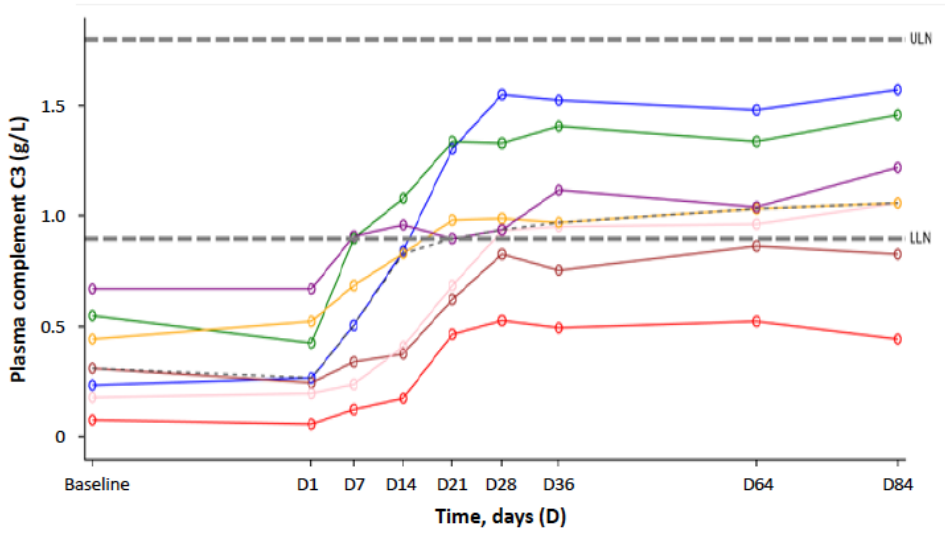
- eGFR stabilization




Adjusted geometric mean (80% CI) of ratio to baseline for UPCR (24h urine collection) over time (N=12)




Evolution of plasma complement C3 over time




Abstract: SU-OR39 ASN 2020

- Pegcetacoplan – C3 Inhibitor (P2)

5 Patients

| | 24-hour uPCR, mg/mg Mean (SE) [range] N = 5 | Serum albumin, g/dL Mean (SE) [range] N = 5 | Serum C3, mg/dL Mean (SE) [range] N = 5 | Serum Creatinine, mg/dL Mean (SE) [range] N = 5 |
|---|---|---|---|---|
| Baseline* | 3.48 (0.82) [1.74, 6.55] | 3.50 (0.30) [2.40, 4.10] | 61.60 (20.42) [11.00, 116.00] | 1.48 (0.50) [0.55, 2.92] |
| Week 48 | 0.93 (0.27) [0.34, 1.69] | 4.08 (0.24) [3.30, 4.60]# | 252.00 (52.82) [82.00, 407.00]# | 1.32 (0.38) [0.50, 2.49]# |

- 65% reduction in 24 hour UPCR at 48 weeks

Abstract: PO1852 ASN 2020

# Considerations

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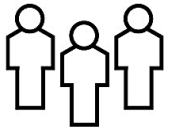
- Stage of disease
  - Some trials with have GFR cutoffs
- Acuity of disease
  - Placebo versus no placebo
- Number of biopsies
  - Nearly all trials will have at least 2
- Number of visits/time at study site
  - Distance to study site
- Ability to stay on a given agent if it is effective for you

| | Phase I | Phase II | Phase III | Phase IV |
|---|---|---|---|---|
| **Number of participants**  | **20–80** participants | **100–300** participants | **1,000–3,000** participants | **Thousands** of participants |
| **Duration**  | Up to **several** months | Up to **two** years | **One–four** years | **One** year + |
| **Purpose**  | Investigates the safety profile of the drug and aims to identify a safe dose that can be used in humans<br><br>**Dose** | Investigates the safety of the drug at the dose selected for use in humans and looks for signs of efficacy<br><br>**Safety and Efficacy** | Investigates both safety and efficacy of the selected dose, often comparing against standard treatment<br><br>**Comparison to Standard of Care** | Investigates long-term effectiveness, benefits and cost effectiveness of treatment. Phase IV trials are conducted once a medicine has been approved for use and is on the market |

Clinicians Considerations: Impression of Efficacy and Safety

# Thank You