Iptacopan (LNP023): a novel oral complement alternative pathway factor B inhibitor safely and effectively stabilises eGFR in C3 glomerulopathy

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58th ERA-EDTA Congress

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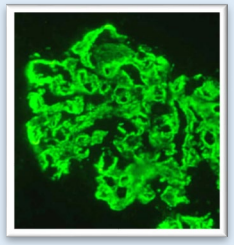
Disclosures

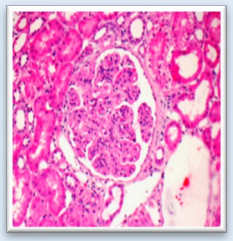
- Received fees for consultation / speakers bureau from Alexion Pharmaceuticals, Biocryst and Novartis.

C3 Glomerulopathy (C3G) - Background

- C3G is a rare disease caused by uncontrolled activation of the complement alternative pathway (AP) in the fluid phase



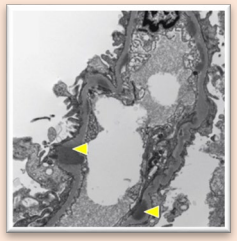
Defined by bright staining for C3 in renal biopsy (≥2x greater than any other immune reactant)[1]



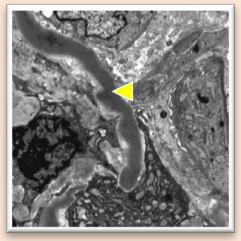
Patterns of inflammation on light microscopy including membrano-proliferative glomerulonephritis[1,2]

Images from Sethi et al. 2009[1]

- 2 subtypes based on appearance in electron microscopy findings



C3GN, with light, hump-like, and clustered deposits in the mesangium, subendothelial and/or subepithelial spaces (yellow arrows)



DDD, with linear dense deposits (yellow arrows)

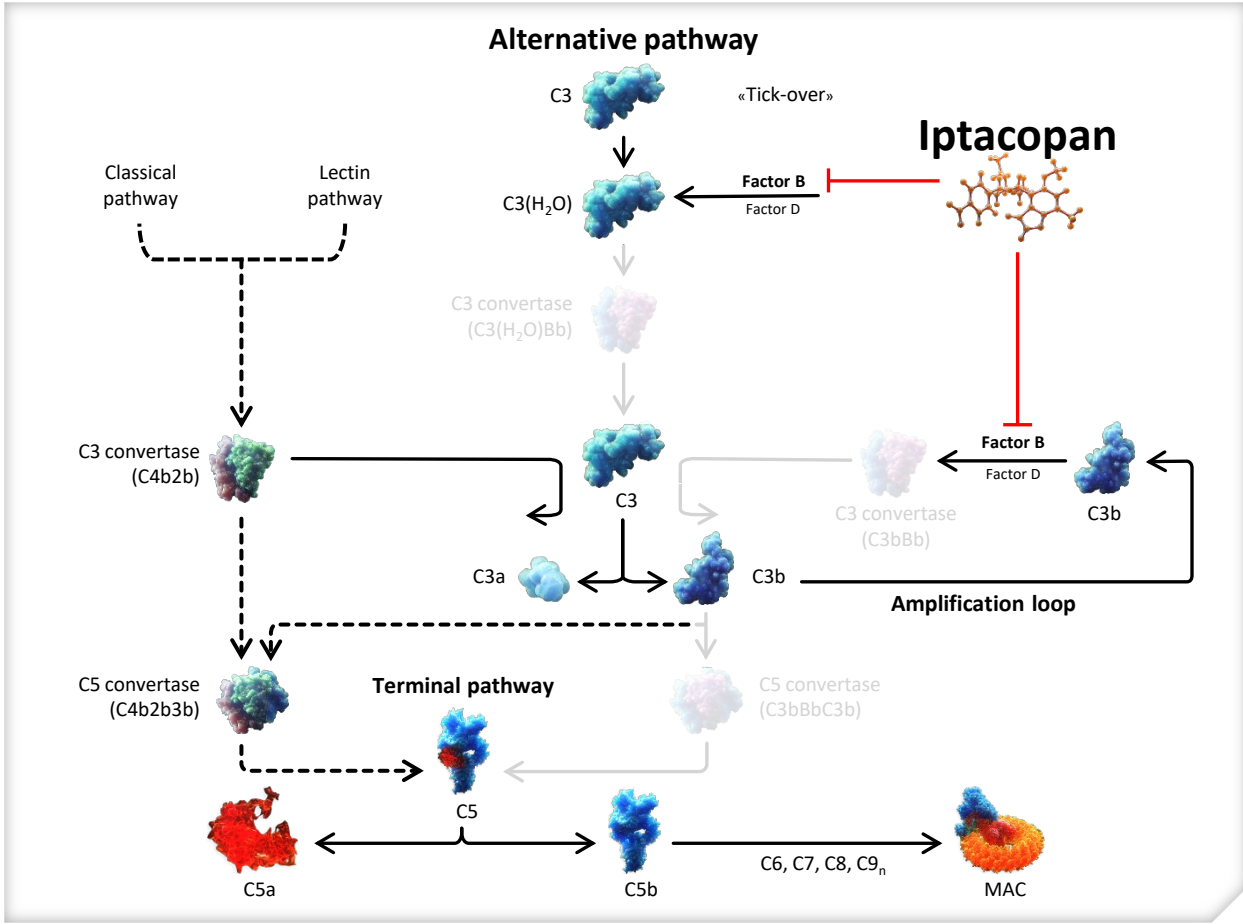
Micrographs from Barbour et al 2013[3]

- C3G affects individuals of all ages, with a median age at diagnosis of 23 years[3, 4]
- Individuals with C3G typically present with hematuria, proteinuria, and low levels of the complement component C3[3, 4]
- There are no approved therapies[5]
- Spontaneous remission of C3G is uncommon, and ~50% of affected individuals develop kidney failure within 10 years of diagnosis[6,7]

C3GN, C3 glomerulonephritis; DDD, dense deposit disease

1. Sethi S, et al. Kidney Int. 2009; 2. Smith RJH, et al. Nat Rev Nephrol. 2019; 3. Barbour TD, et al. Semin Nephrol 2013;
4. Martin B, Smith JH. GeneReviews®. Accessed March 4, 2021. https://www.ncbi.nlm.nih.gov/books/NBK1425 (Updated April 5, 2018);
5. Caravaca-Fontán F, et al. Nephron 2020; 6. Goodship TH, et al. Kidney Int. 2017;
7. Medjeral-Thomas NR, et al. Clin J Am Soc Nephrol. 2014.

Iptacopan: A unique MoA to prevent activation of the alternative complement pathway



Iptacopan, an inhibitor of Factor B

- Blocks the AP pathway amplification by binding to factor B
- Prevents activity of C3 convertase and, subsequently, the formation of C5 convertase in the AP
- Blocks amplification of the lectin and classical pathways
- Direct signalling from the lectin and classical pathways remains
- Inhibits opsonization, anaphylatoxins and MAC formation via AP

AP, alternative pathway; C3G, C3 glomerulopathy; MAC, membrane attack complex; MoA, mechanism of action

Smith RJH, et al. Nat Rev Nephrol. 2019
Schubart A, et al. PNAS 2019

Iptacopan in C3G: Phase 2 Study design (NCT03832114)

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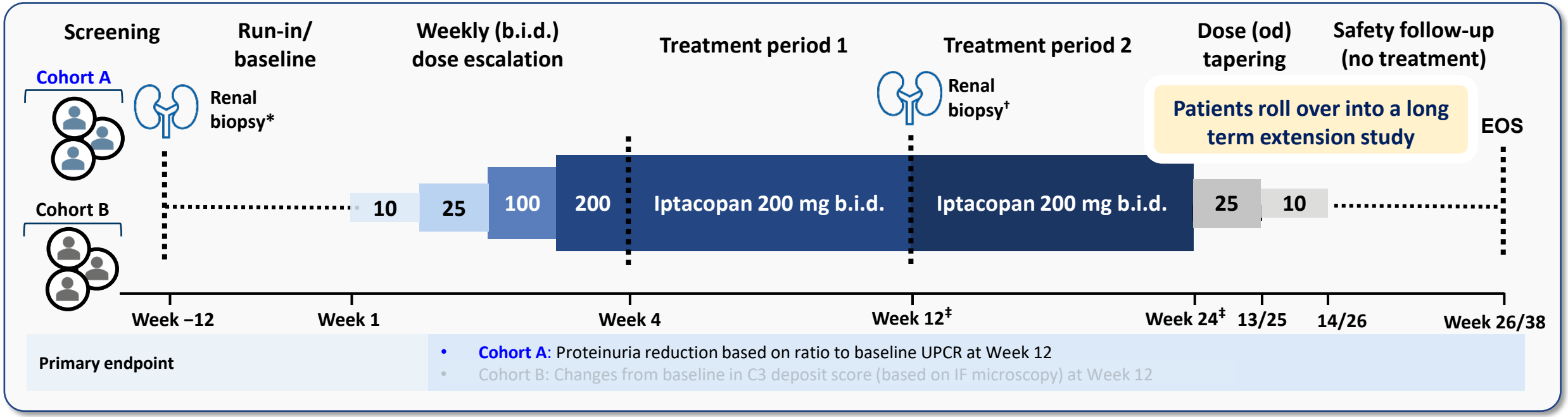
Primary objective: To evaluate the efficacy of iptacopan in **reducing proteinuria** at Week 12 measured as ratio to baseline of UPCR (derived from 24h urine sample)

Key inclusion criteria:

- **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

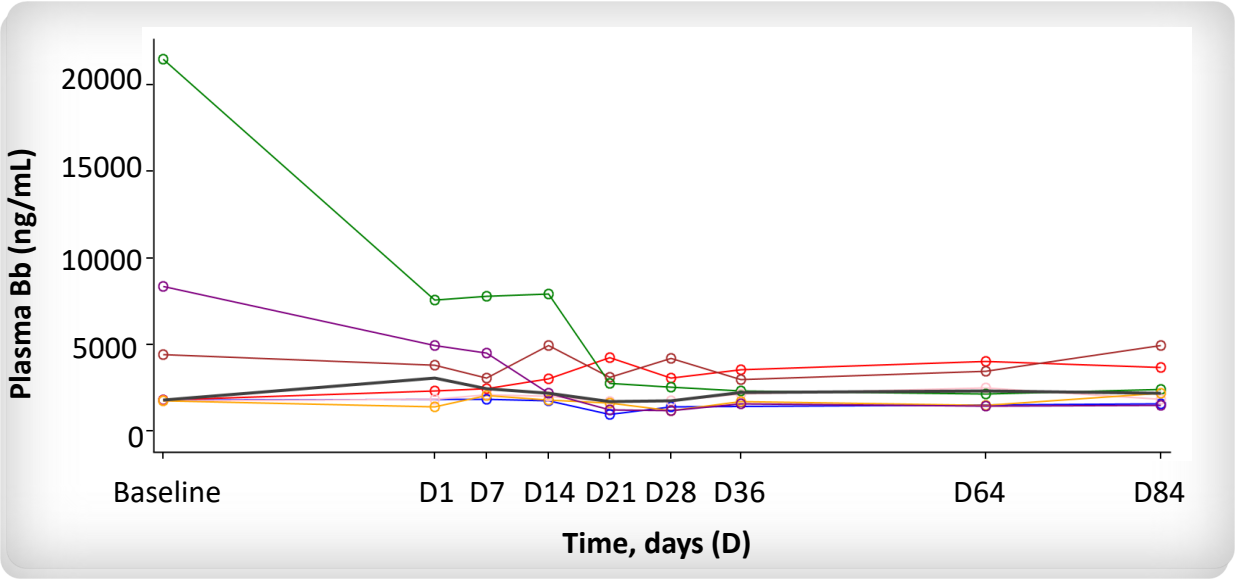


*Not required for Cohort A unless most recent biopsy material >12 months old; †Optional for Cohort A;
‡Patient may roll over into a separate extension study (CLNP023B2001B) at Week 12; Planned study start and completion dates are subject to change. bid, twice a day; C3G, C3 glomerulopathy; EOS, end of study; IF, immunofluorescence; od, once daily; UPCR, urinary protein to creatinine ratio.

https://clinicaltrials.gov/ct2/show/NCT03832114.
Accessed 06 Apr, 2021.

Inhibition of alternative pathway activity and pharmacokinetic profile following 12 weeks of iptacopan

Changes in plasma Bb levels over time



PK parameter (Unit)	10 mg b.i.d. N= 7	25 mg b.i.d. N= 6	100 mg b.i.d. N= 6	200 mg b.i.d. N= 6
AUC_{last} (hr*ng/mL)	4030 ± 556 (13.8%)	6180 ± 2310 (37.4%)	15200 ± 5840 (38.4%)	22300 ± 11100 (49.9%)
C_{max} (ng/mL)	700 ± 104 (14.8%)	1060 ± 407 (38.5%)	2580 ± 1120 (43.6%)	3990 ± 1770 (44.4%)
C_{min} (ng/mL)	297 ± 97.5 (32.8%)	493 ± 146 (29.6%)	1210 ± 451 (37.2%)	1680 ± 729 (43.4%)
T_{max} (hr)	2.00 (1.00 - 6.00)	2.00 (1.00 - 6.00)	2.00 (0.500 - 4.00)	2.00 (1.00 - 4.00)

Statistics are Mean ± SD (CV%); For T_{max}: Median (Min-Max)

- The **inhibition of AP** activity was demonstrated in both urine and blood complement markers upon treatment with iptacopan, with maximal effects observed at 200 mg b.i.d.

- Iptacopan 200 mg b.i.d dose reached the mean C0 target trough level ≥900 ng/mL.

AP, alternative pathway; b.i.d, twice daily; min, minimum; max, maximum; PK, pharmacokinetics

Wong et al (2020): Oral Presentation. ASN 2020 Meeting – October 2020

Iptacopan treatment led to an improvement in C3 levels and reduction in sC5b-9 levels (N=7)

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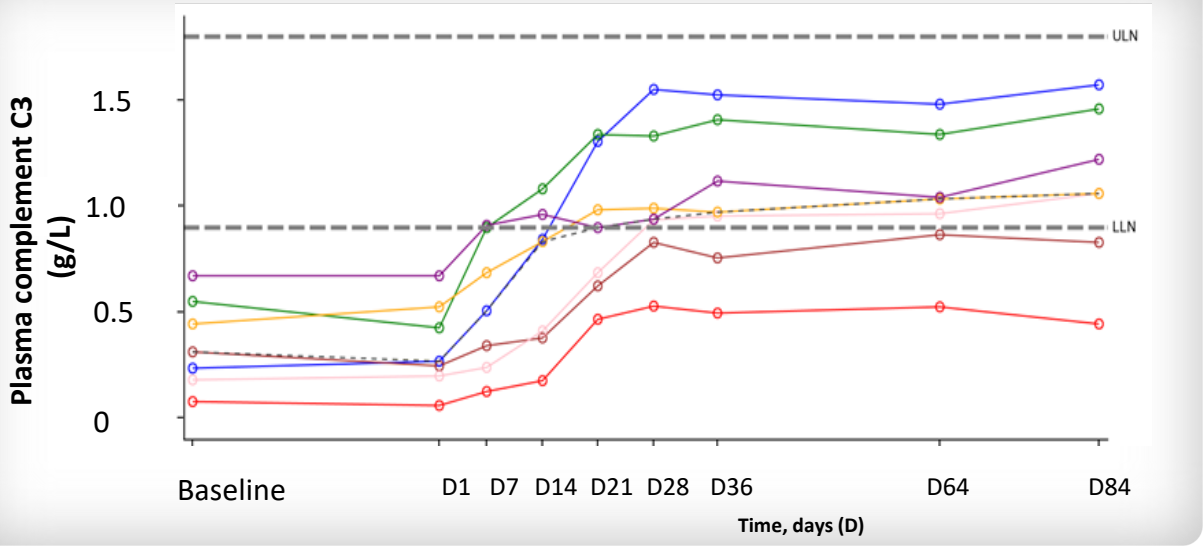
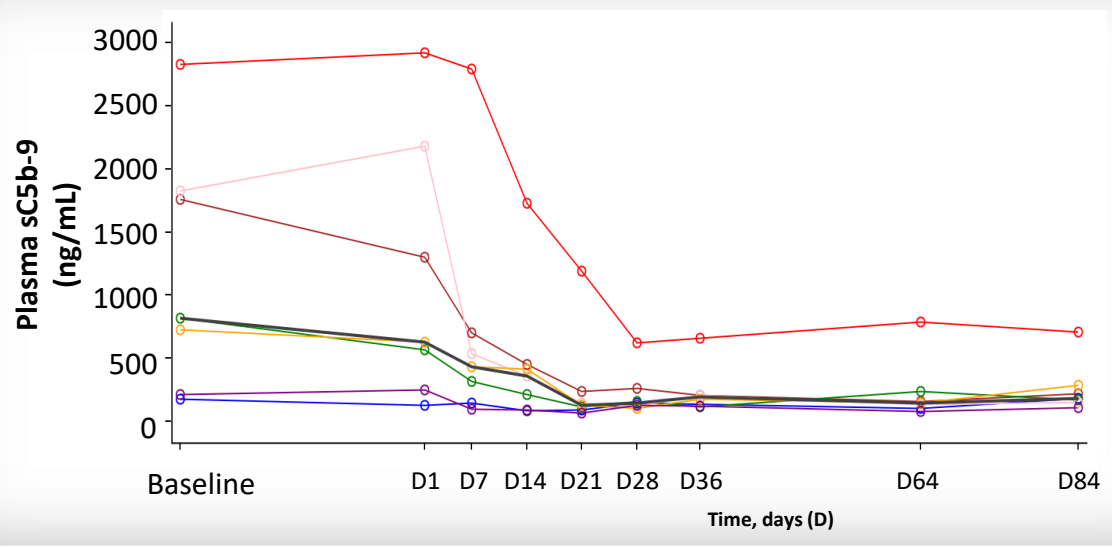
Changes in plasma complement C3 over time



Upper and lower limits of normal for plasma C3

Median value

Changes in plasma sC5b-9 levels over time



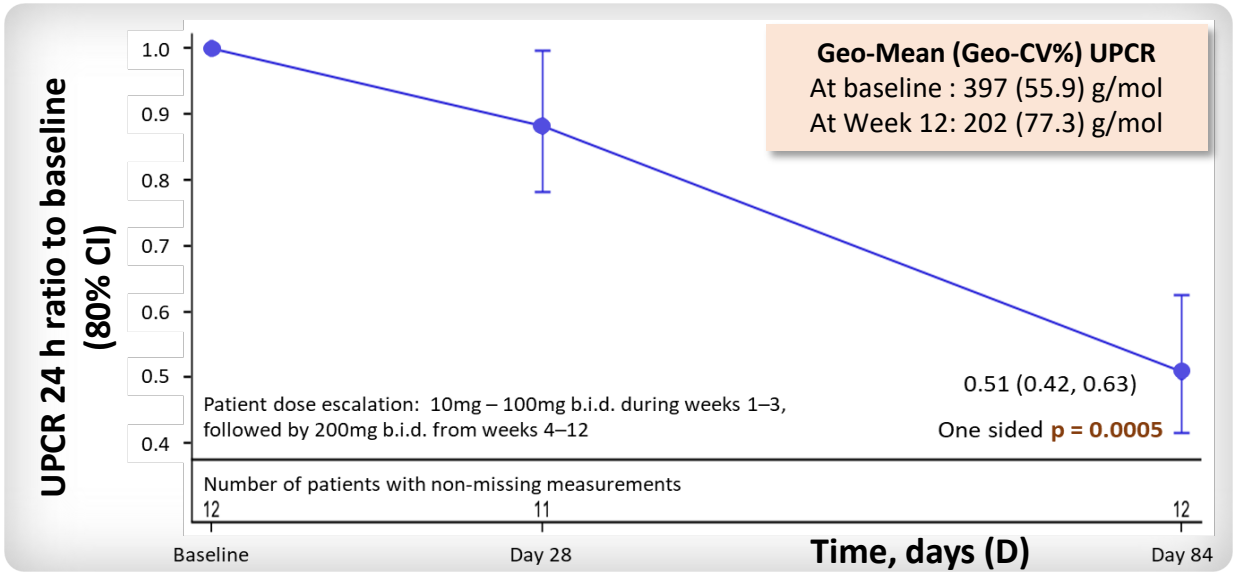
- There was a uniform improvement in serum C3 levels with normalization in 71% of patients (n=7).
- Marked reduction (and normalization) of plasma and urine soluble C5b-9 (SC5b-9, the soluble membrane attack complex) levels were observed in 7 patients with elevated baseline levels

CI, confidence interval; LLN, lower limit of normal; ULN, upper limit of normal

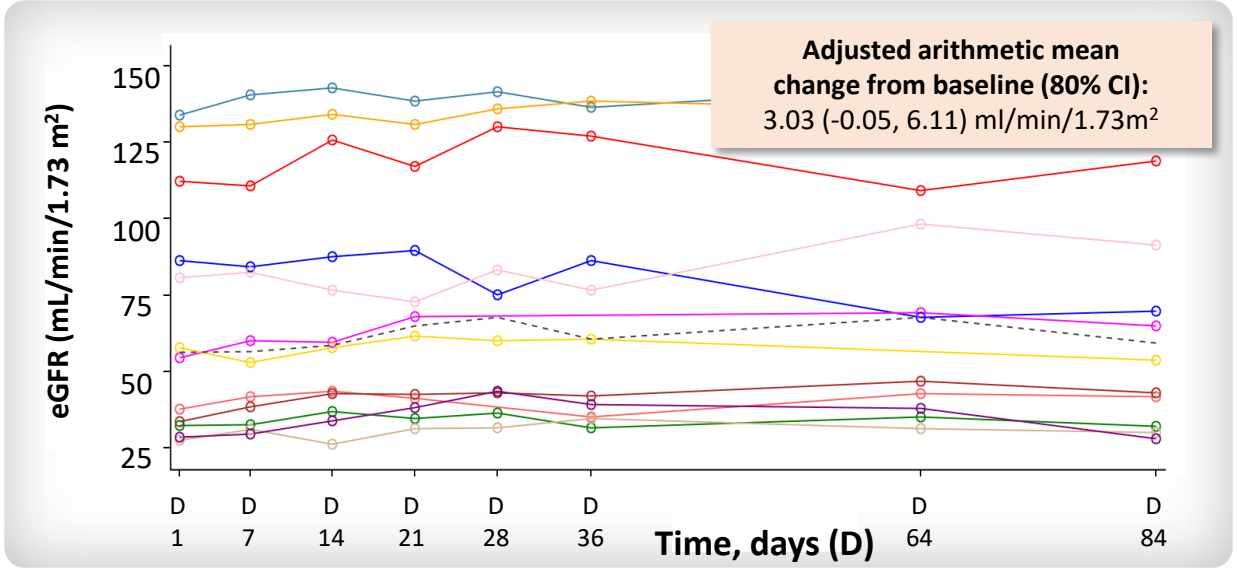
Wong et al (2020): Oral Presentation. ASN 2020 Meeting – October 2020

Reduced proteinuria and eGFR stability following treatment with iptacopan for 12 weeks

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



eGFR over time



Baseline is defined as the last available assessment (ie., Day 1, 0 hr pre dose) prior to the first dose of study drug. Dotted line represents median value

- A 12 week course of iptacopan resulted in a 49% reduction in proteinuria (n=12)
- Individual patient data demonstrates eGFR stability across a wide range of kidney function (n=12)

b.i.d, twice daily; CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; UPCR, Urine Protein to Creatinine concentration Ratio

Wong et al (2020): Oral Presentation. ASN 2020 Meeting – October 2020

Extending iptacopan treatment to 6 months resulted in 56% reduction in proteinuria compared with baseline and stability of eGFR

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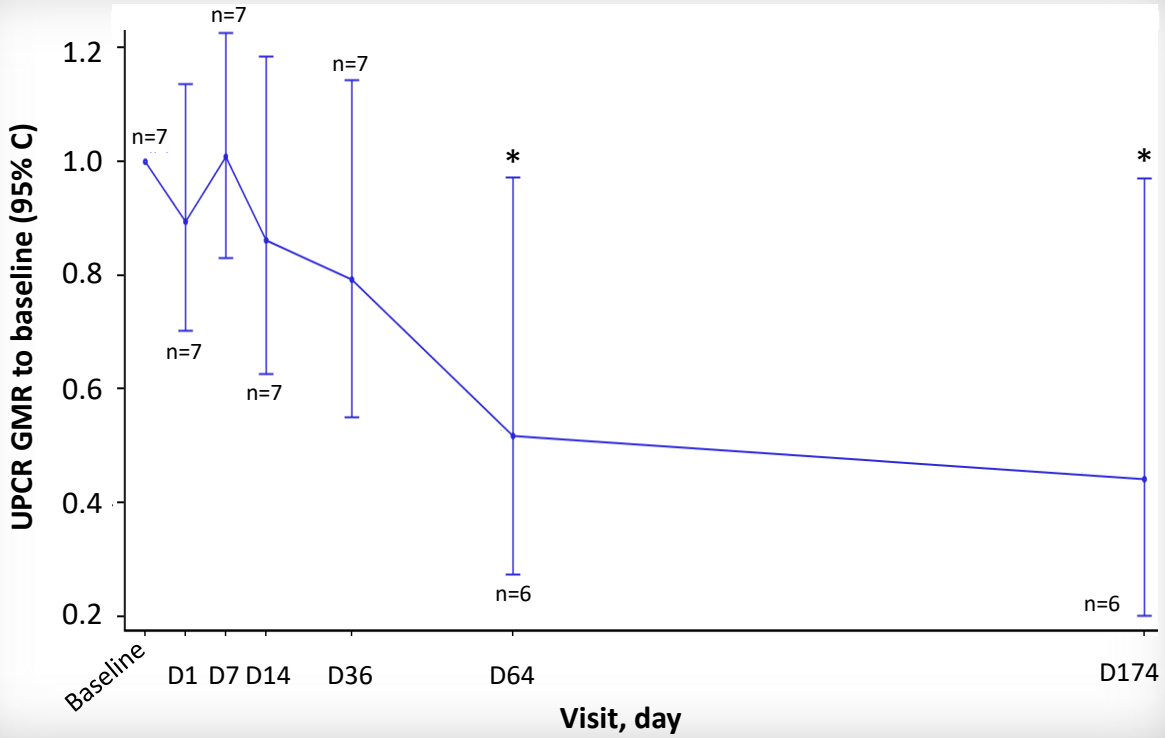
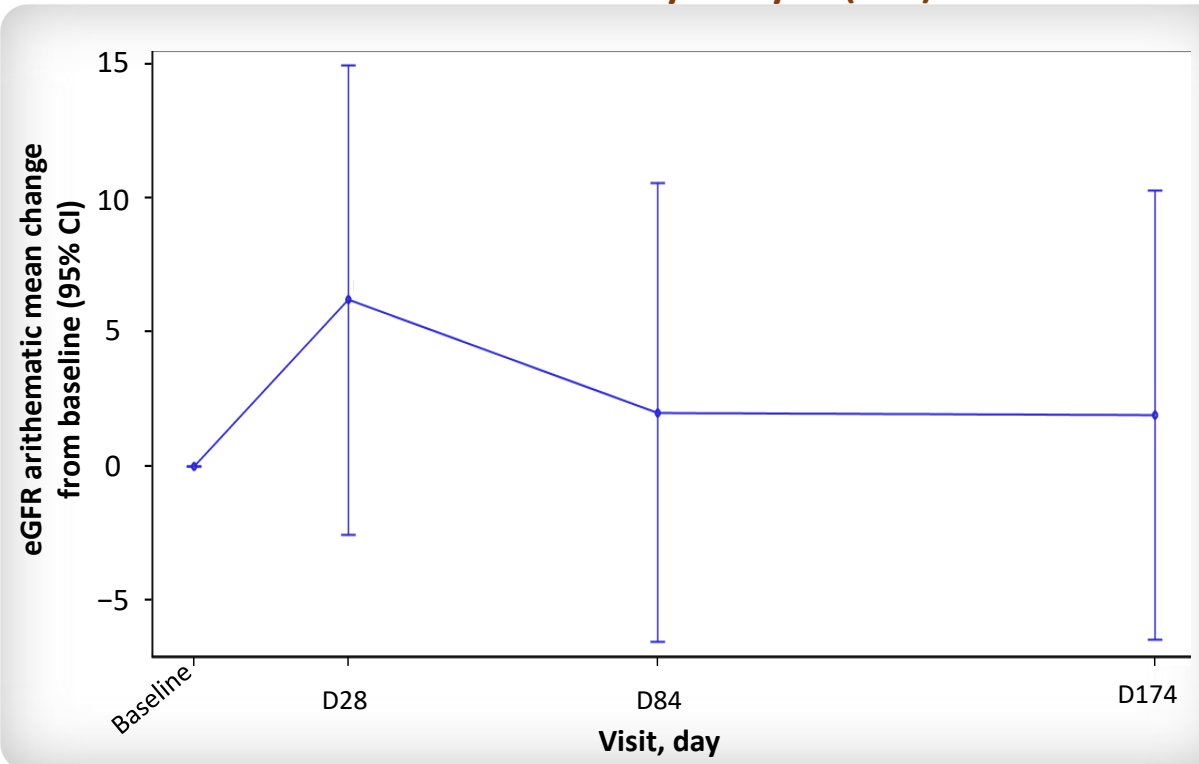
Unadjusted geometric mean (95% CI) ratio to baseline for UPCR (FMV urine collection) over time



Arithmetic mean (95% CI) eGFR change from baseline sensitivity analysis (n=7)



*p<0.05

D174: D90 (extension) + D84

Data from 7/12 patients who received an additional 3 months of iptacopan treatment in the extension study (total of 6 months follow-up): 6/7 had UPCR assessments at Month 6.

CI, confidence interval; eGFR, estimated glomerular filtration rate; FMV, first morning void; UPCR, Urine Protein to Creatinine concentration Ratio

Wong et al (2020): Oral Presentation. ASN 2020 Meeting – October 2020

Iptacopan showed a favourable patient safety profile following 12 weeks of treatment

- No deaths reported
- No SAEs related to iptacopan
- No AEs leading to iptacopan discontinuation in this patient cohort

Overall AE incidence*	Number, patients [N=16]
AE, Patients with AE	38, 12
Mild AE	31, 11
Moderate AE	6, 3
Severe AE	1, 1
Study drug-related AE	2, 2
Serious AE (not related to study drug)	1, 1
AE leading to discontinuation of study treatment	0
Study-drug related AE leading to discontinuation of study treatment	0

*This data includes all 16 patients enrolled as of 13-Jul-2020 up to the interim analysis, but excludes any data from the extension study

AE, adverse event; SAE, serious adverse event

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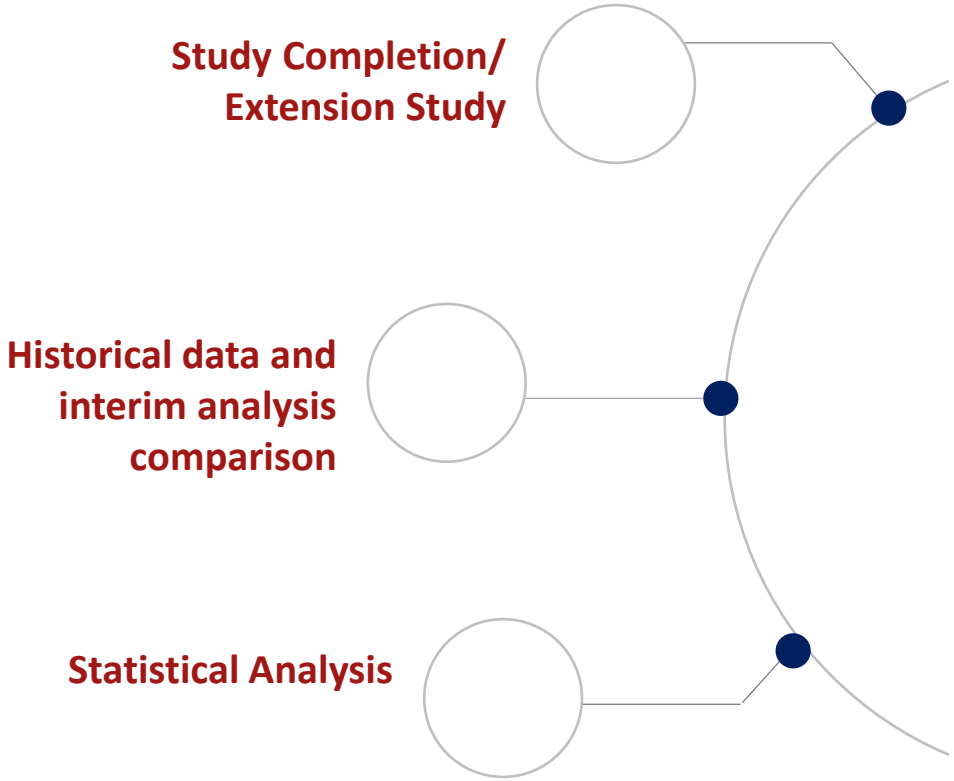
The **aim** of this analysis was to determine whether iptacopan treatment altered eGFR slope in this same population



On study completion all patients received ongoing iptacopan in a long-term extension study [1]

Historical data were collected on eGFR (CKD-EPI) for the two-year period prior to patients entering the study or since diagnosis where this was less than two years, and were compared with those obtained in the IA following the commencement of iptacopan

A generalized linear mixed model, with a common intercept, a pre-treatment slope and a change in the slope following iptacopan treatment was used to predict the pre-post iptacopan change in eGFR over time

1. https://clinicaltrials.gov/ct2/show/NCT03955445.Accessed 28 Apr, 2021.

Patient demographics

Characteristic		12 Patients (11 C3GN, 1 DDD)
Age (years)	Mean (SD), range	26.1 (12.1), 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 $(kg/m)^2$	Mean (SD)	22.2 (2.7)
Estimated GFR ($mL/min/1.73m^2$)	Geo-mean (CV %) Median Range	57.9 (65.46) 56.2 28–134
Urine protein:creatinine ratio (g/moL)*	Geo-mean (CV %) Median Range	397.4 (56.0) 359 221–1019

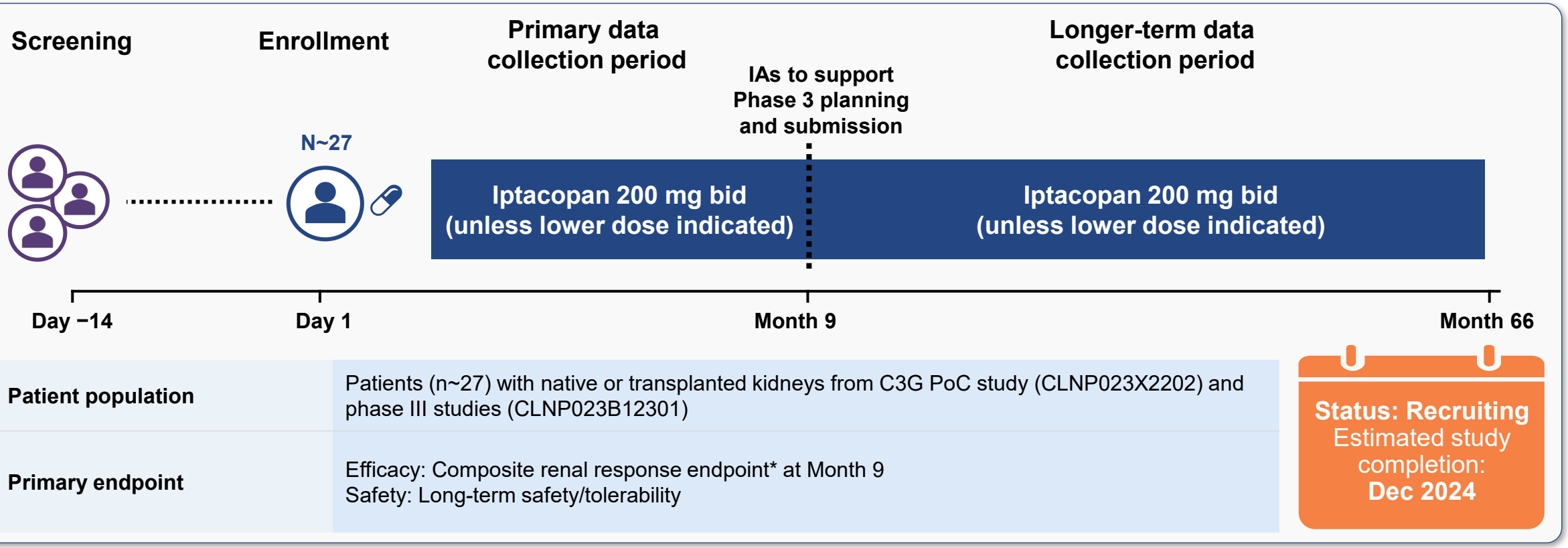
*24-hour urine collection

C3GN, C3 glomerulonephritis; CV, coefficient of variation; DDD, dense deposit disease; GFR, glomerular filtration rate; Geo-CV, geometric coefficient of variation; IA, interim analysis; SD, standard deviation.

Wong et al (2020): Oral Presentation. ASN 2020 Meeting – October 2020

C3G extension –Study design

An open-label, non-randomized extension study to evaluate the long-term efficacy, safety and tolerability of Iptacopan (NCT03955445)



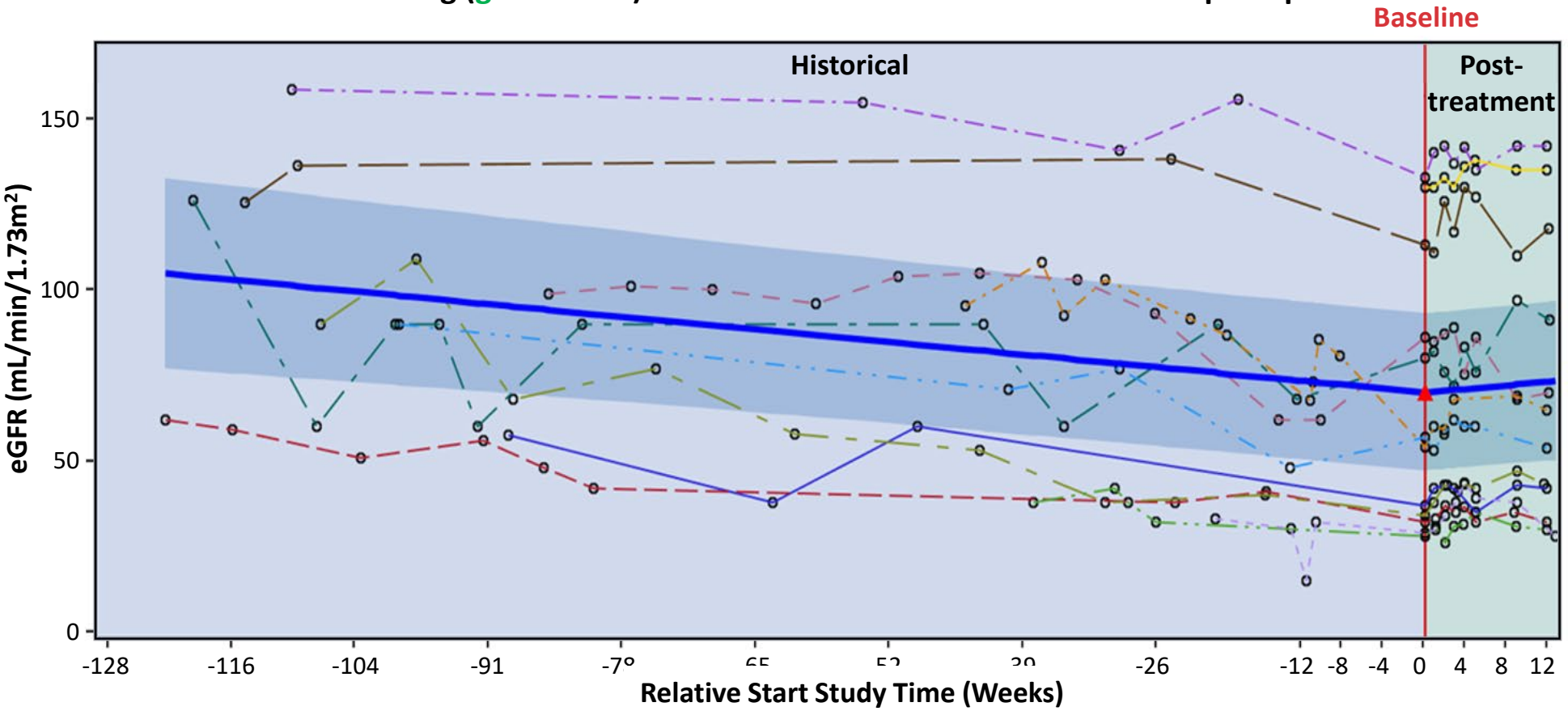
Patient population	Patients (n~27) with native or transplanted kidneys from C3G PoC study (CLNP023X2202) and phase III studies (CLNP023B12301)
Primary endpoint	Efficacy: Composite renal response endpoint* at Month 9 Safety: Long-term safety/tolerability

Status: Recruiting
Estimated study completion:
Dec 2024

Planned study start and completion dates are subject to change
*eGFR, proteinuria and complement biomarker components
bid, twice a day; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IA, interim analysis; PoC, proof of concept.
https://clinicaltrials.gov/ct2/show/NCT03955445. Accessed Feb 22, 2021.

12 weeks treatment with iptacopan 200mg b.i.d resulted in a statistically significant and clinically important improvement in eGFR slope

Individual patient eGFR slopes (n=12) for up to 2 years prior to (blue zone) and following (green zone) commencement of 12 week course of iptacopan



- Treatment with iptacopan was associated with a mean increase in eGFR of 3.1 mL/min/1.73m^2 from baseline to 12 weeks
- This corresponds to a mean predicted eGFR preservation of 6.4 mL/min/1.73m^2 over 12 weeks as a result of iptacopan administration (p=0.0459)

Mean eGFR slope and 95% CI indicated by **bold blue line** and surrounding shadowed area.

CI, confidence interval; eGFR, estimated glomerular filtration rate

Wong E et al. 2021. ERA-EDTA 2021 congress

Conclusions and clinical implications

We have previously shown that extended iptacopan treatment up to 25 weeks has resulted in:
- ongoing stability of eGFR in patients with C3G
- and a favourable safety and tolerability profile

Here we show that treatment with iptacopan 200 mg b.i.d over a 12 week period showed **statistically significant** and **clinically important** improvements in eGFR slope in patients with C3G

These results suggest that iptacopan may slow down progression to, or even potentially prevent development of, kidney failure in patients with C3G

b.i.d, twice daily; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate