Final 12-week Endpoint Analyses of a Phase 2 Dose-Ranging Study to Investigate the Efficacy and Safety of Iptacopan in Primary IgA Nephropathy

Professor Jonathan Barratt

on behalf of the Iptacopan IgAN Program Steering Committee

University of Leicester & John Walls Renal Unit, Leicester, UK

58th ERA-EDTA Congress, Berlin, June 5–8, 2021

Disclosures

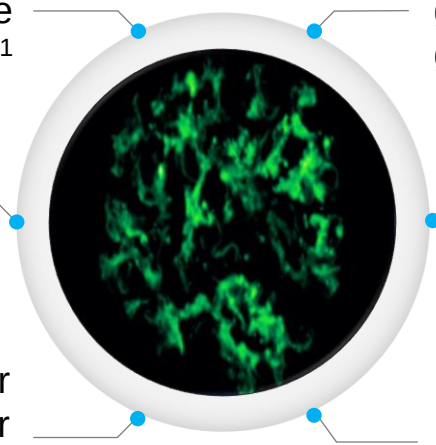
Prof. Barratt reports co-chairing the Steering Committee for iptacopan trials in IgAN

Introduction: IgA nephropathy

Characterized by deposits of IgA1-containing immune complexes in the glomerular mesangium[1]

Key clinical manifestations include proteinuria, hematuria, hypertension and/or elevated creatinine[2]

Kidney biopsies stain positive for components of AP and, less often, for LP; deletions in *CFHR1/3* gene protects from developing IgAN[3-5]



Most common form of primary glomerulonephritis worldwide with a global incidence of ~25/million/year[6]

Up to 50% of patients with IgAN may develop kidney failure and require dialysis; 60% of patients with kidney failure will need ≥1 kidney transplant[7,8]

Supportive care (with ACEi/ARB) remains the basis of management of IgAN[9,10]

There are no effective and well-tolerated targeted therapies approved for IgAN that slow or prevent progression to kidney failure[9,10]

ACEi, angiotensin-converting enzyme inhibitor; AP, alternative pathway; ARB, angiotensin receptor blocker; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; LP, lectin pathway; CFHR, complement factor H related protein

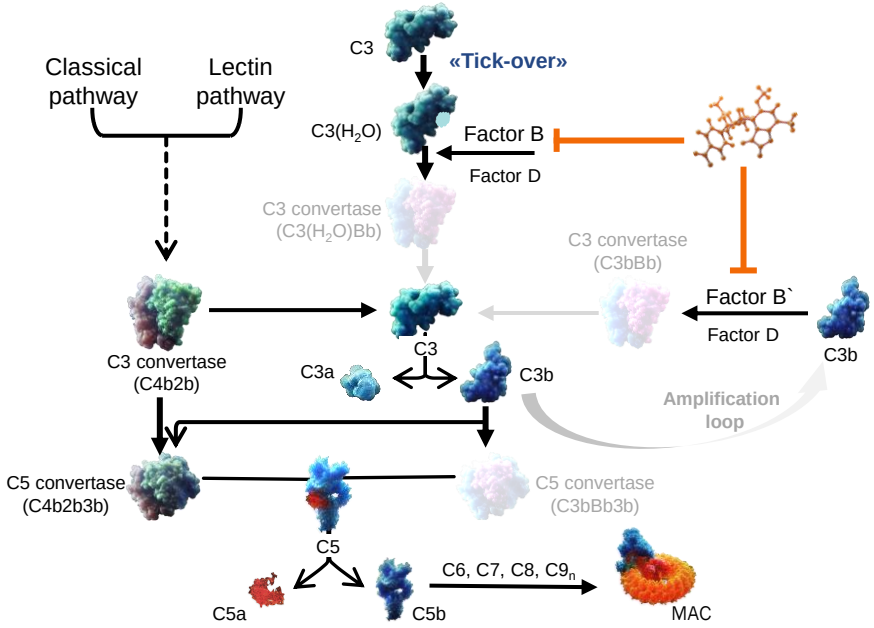
1. Roberts ISD et al., Nat Rev Nephrol 2014;10:445–454; 2. Floege J, Eitner F. J Am Soc Nephrol 2011;22:1785-1794; 3. Rizk DV et al. Front Immunol 2019;10:504 (doi: 10.3389/fimmu.2019.00504); 4. Medjeral-Thomas NR et al. Adv Chronic Kidney Dis 2020;27:111-119; 5. Gharavi AG et al., Nat Rev Gent. 2011; 43:321-327; 6. McGrogan A et al. Nephrol Dial Transplant 2011;26:414-430; 7. Barbour, Reich. Curr Opin Nephrol Hypertens 2018; 8. Wyatt RJ, et al. 2013 N Engl J Med 368:2402-2414; 9. Reich HN et al. J Am Soc Nephrol 2007;18:3177-3183; 10. Gutiérrez E et al. Nephron 2020;144:555-571.

Figure adapted from Ref 1

This scientific information may include data/information on investigational uses of compounds/drugs that have not yet been approved by regulatory authorities.

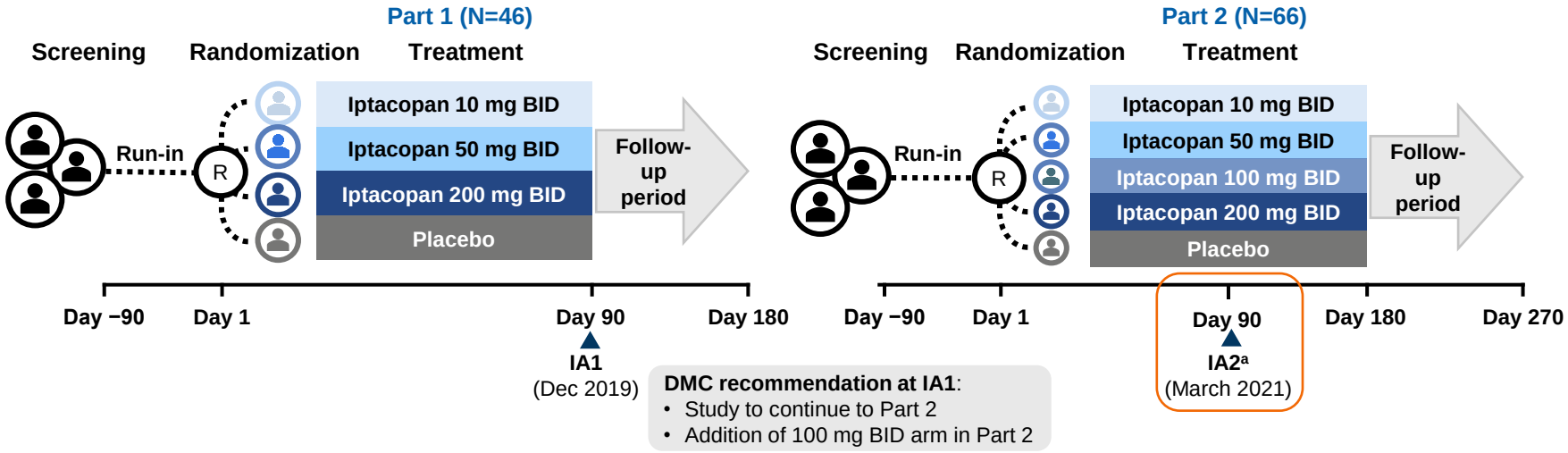
Introduction: Rationale for use of iptacopan in IgAN

- **Iptacopan (LNP023)** is an oral, first-in-class, highly potent, selective small-molecule **inhibitor of factor B (FB)**
- Iptacopan **binds to FB** and its catalytically active fragment Bb to **suppress the activity of AP C3 convertase** and, thus, activation of the amplification loop
- This **prevents** downstream **generation of the AP C5 convertase complex**, opsonization, and formation of C5a anaphylatoxins and membrane attack complex
- Iptacopan was safe, and well tolerated in first-in-human studies
- Given the role of AP in the pathogenesis of IgAN, inhibition of AP with iptacopan may provide an attractive therapeutic strategy to halt the disease progression



AP, alternative pathway; FB, factor B; IgAN, immunoglobulin A nephropathy; MAC, membrane attack complex
Schubart A et al. Proc Natl Acad Sci U S A 2019;116(16):7926-7931.

Study design



Study design	• An adaptive seamless randomized, double-blind, placebo-controlled, dose-ranging study
Primary objective	• To evaluate the dose response relationship of iptacopan on the reduction in proteinuria versus placebo after 90 days of treatment
Secondary objectives	• Safety and tolerability of iptacopan, eGFR, and biomarkers reflecting activity of the alternative complement pathway

[a]Analysis includes patients pooled from parts 1 and 2 of the study (N=112)

BID, twice daily; DMC, data monitoring committee; eGFR, estimated glomerular filtration rate; IA, interim analysis; R, randomization

https://clinicaltrials.gov/ct2/show/NCT03373461 (Last accessed: 20 April 2021).

Key eligibility criteria

Key inclusion criteria

- Age ≥18 years with biopsy-verified IgAN within the prior 3 years
- UPCR of ≥0.8 g/g or urine protein of ≥0.75 g/24h at screening and urine protein of ≥0.75 g/24h at the end of run-in period
- eGFR of ≥30 mL/min/1.73 m^2
- Body weight of ≥35 kg; BMI of 15–38 kg/m^2
- On supportive care including a maximally tolerated dose of an ACEi/ARB, antihypertensive therapy, or diuretics for ≥90 days before study treatment
- Vaccination against *Neisseria meningitidis, Streptococcus pneumonia*[#], and *Haemophilus influenza*[#]

Key exclusion criteria

- Crescent formation in ≥50% of glomeruli
- Previous treatment with immunosuppressive agents* within 90 days of starting the study treatment
- Patients with transplanted organs
- History of immunodeficiency diseases or HIV positive
- Chronic infection with HBV or HCV
- History of severe allergic reactions, malignancy of any organ system, porphyria metabolic disorder, or drug or alcohol abuse
- Any surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of the drugs

[#]If available, and as per local regulations; *Cyclophosphamide or mycophenolate mofetil, or cyclosporine, systemic corticosteroids.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; UPCR, urine protein-to-creatinine ratio
https://clinicaltrials.gov/ct2/show/NCT03373461 (Last accessed: 8 April 2021).

Baseline characteristics and demographics

- Treatment groups were mostly balanced in terms of demographics and baseline characteristics
  - However, at baseline, proteinuria levels were numerically lower in placebo and iptacopan 200 mg BID groups; eGFR was lower in iptacopan 50 mg and 200 mg BID groups

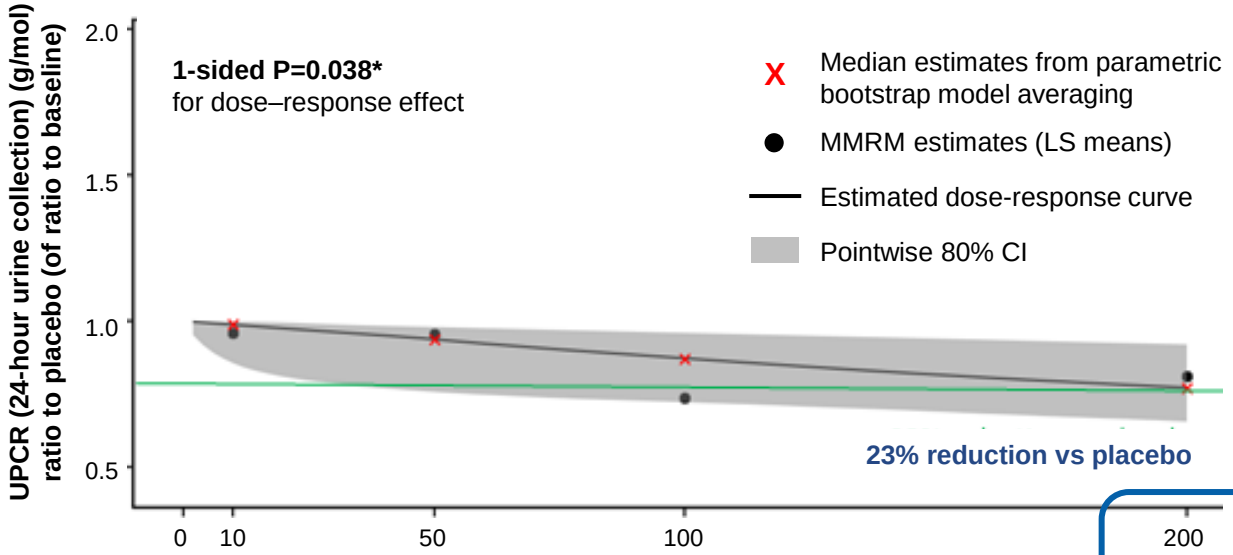
	Iptacopan				Placebo N=25
	10 mg BID N=20	50 mg BID N=19	100 mg BID N=22	200 mg BID N=26	
Age, years	39.2 (12.42)	36.6 (8.42)	36.0 (13.15)	42.5 (15.76)	39.4 (11.00)
Male (%)	45%	68%	50%	58%	72%
Asian ethnicity (%)	45%	47%	55%	46%	44%
BMI, kg/m^2	26.3 (5.51)	25.8 (4.37)	26.1 (4.60)	25.8 (4.44)	25.4 (3.69)
UPCR, mg/mmol*	214.1 (122.29)	188.2 (90.38)	203.4 (98.29)	151.0 (109.46)	146.6 (61.62)
UPCR <200 mg/mmol (%)	55%	53%	68%	85%	80%
eGFR, mL/min/1.73 m^2	66.0 (28.51)	53.8 (22.73)	67.0 (31.75)	57.9 (28.92)	65.7 (32.60)
SBP, mmHg	134.4 (11.65)	122.6 (12.15)	125.0 (11.30)	125.7 (11.66)	125.5 (11.37)

Data are mean (SD) unless otherwise specified; *UPCR sampled from a 24-hour urine collection at baseline

BID, twice daily; BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SD, standard deviation; UPCR, urine protein-to-creatinine ratio

Iptacopan showed dose-dependent reduction in proteinuria at Day 90 versus placebo

- Treatment with **iptacopan 200 mg BID** led to a **23%** (80% CI: 8%, 34%) **reduction in** 24-hour **UPCR** at 90 days
  - **A significant dose–response effect** of iptacopan versus placebo (1-sided P=0.038*) was observed
  - Iptacopan treatment was associated with a trend toward **lower first morning void UPCR levels**

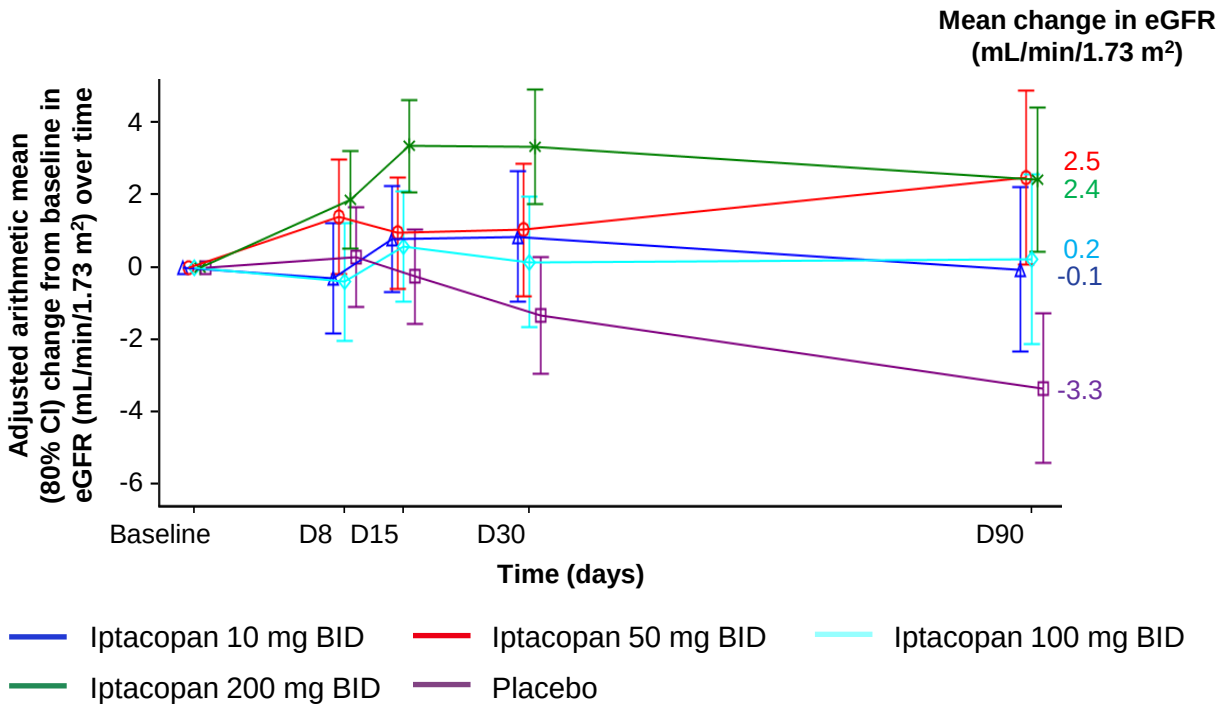


*Multiplicity-adjusted P-value; analysis adjusted for baseline UPCR (24-hour) and ancestry

BID, twice daily; CI, confidence interval; LS, least squares; MCP-mod, Multiple Comparison Procedure – Modelling; MMRM, mixed model repeated measurements; UPCR, urine protein-to-creatinine ratio

Treatment with iptacopan was associated with stabilization of eGFR

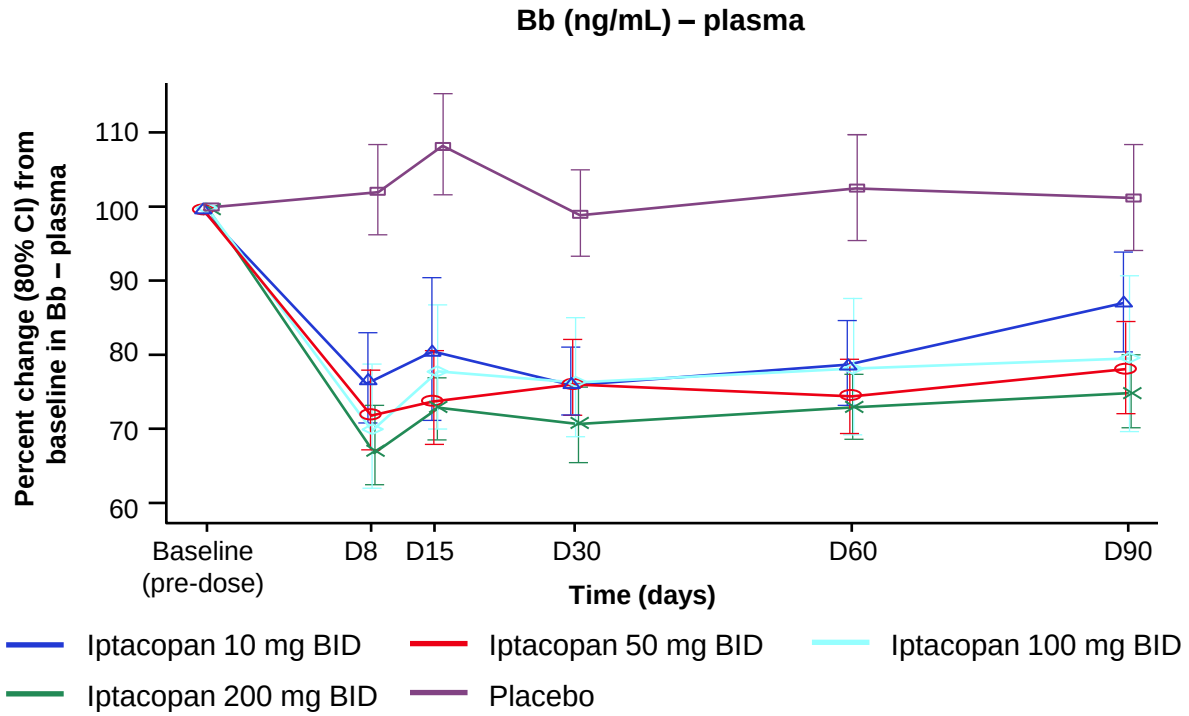
- **eGFR** showed a **trend towards stabilization with** all doses of **iptacopan** compared with a decline in eGFR observed with placebo



BID, twice daily; CI, confidence interval; D, day; eGFR, estimated glomerular filtration rate

Iptacopan reduces levels of alternative pathway biomarkers in plasma

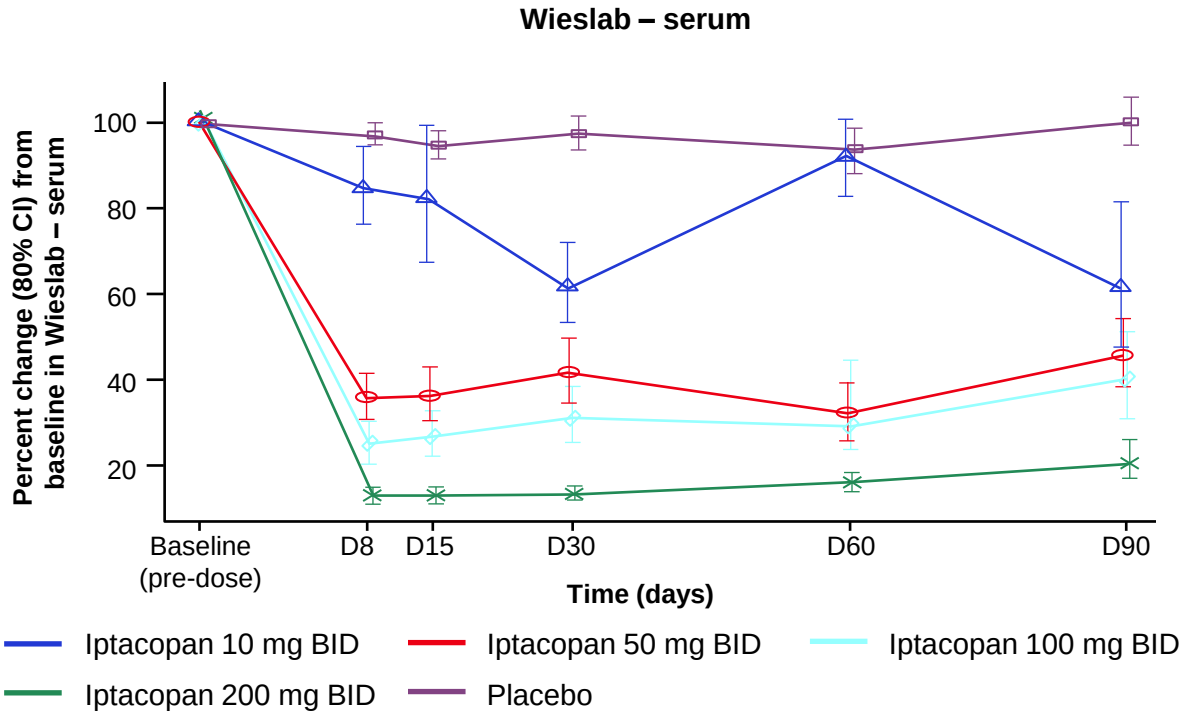
- Formation of Bb (generated by cleavage of FB by FD) represents activation of AP
- **Maximal inhibition with iptacopan was seen from Day 8** onwards



AP, alternative pathway; BID, twice daily; CI, confidence interval; D, day; FB, factor B; FD, factor D

Dose-dependent reduction in serum levels of alternative pathway biomarkers by iptacopan

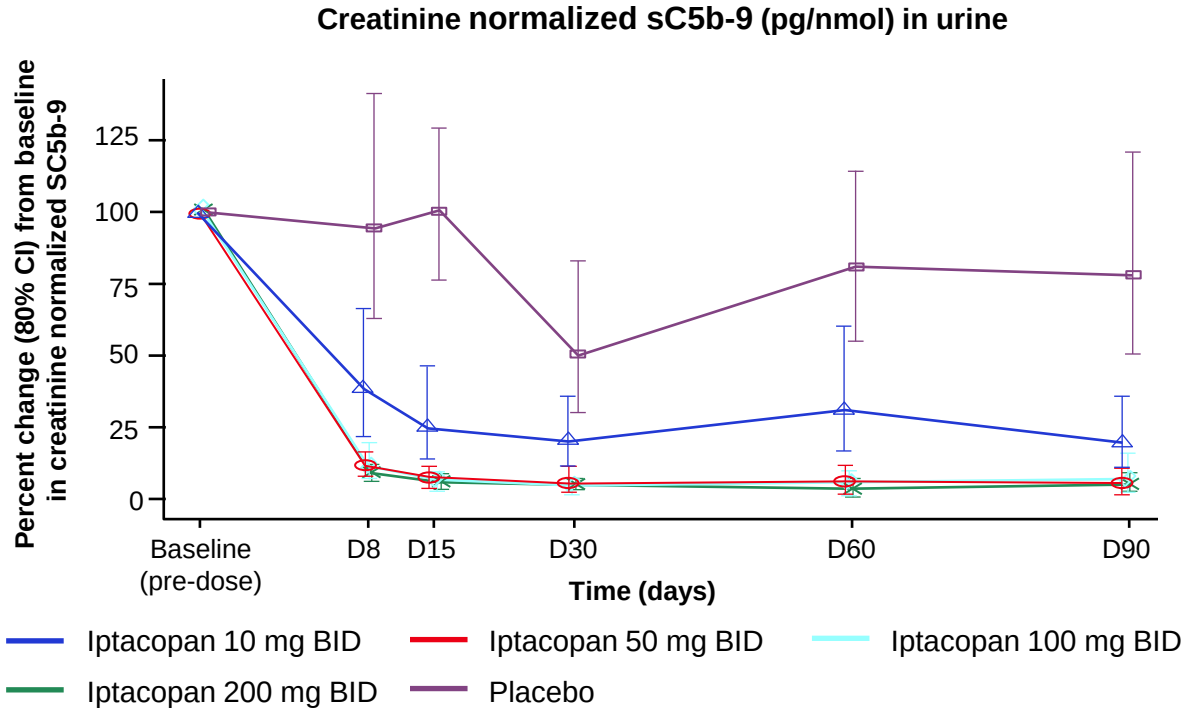
- Dose-dependent **reduction in serum levels of the Wieslab assay** (which measures AP activation) by iptacopan versus placebo
- With iptacopan treatment, **maximal inhibition was seen from Day 8** onwards (with all doses except 10 mg BID)
  - Near **complete inhibition** was observed **with 200mg BID dose**



AP, alternative pathway; BID, twice daily; D, day

Iptacopan reduces levels of alternative pathway biomarkers in urine

- Iptacopan treatment results in **reduction of urinary soluble C5b-9** (reflective of terminal pathway activation and MAC formation) excretion by iptacopan versus placebo
- **Maximal inhibition** with iptacopan treatment was seen **from Day 8** onwards (with all doses except 10 mg BID)



CI, confidence interval; BID, twice daily; D, day; MAC, membrane attack complex; sC5b-9, soluble C5b-9

Iptacopan treatment was well tolerated

- Overall, **61%** of patients experienced **treatment emergent AEs** up to Day 90
- There was **no evidence** of a **dose-dependent occurrence of AEs**; 65% of patients in the iptacopan 10 mg BID group, 68% in 50 mg BID, 55% in 100 mg BID, 54% in iptacopan 200 mg BID and 64% in placebo groups reported at least one AE up to Day 90
- All **treatment emergent AEs** to Day 90 were **mild (92%)** or moderate (8%); the most common AEs were: headache, back pain, diarrhea, nasopharyngitis, and vomiting with no dose response or difference from placebo for any of these
- **No study drug–related serious AEs** and **no deaths** were reported during the study
- Overall, there were **no serious infections** and no infections reported to be caused by encapsulated bacteria

AE, adverse event; BID, twice daily

Summary

- This is the first study to report the safety and efficacy of selective alternative pathway inhibition in IgAN
- Inhibition of alternative pathway activation with iptacopan for 90 days was associated with a significant dose-dependent reduction in UPCR and a trend to eGFR stabilization
  - After 90 days, patients treated with iptacopan 200 mg BID experienced 23% reduction in proteinuria versus placebo
- Iptacopan treatment was well tolerated and resulted in inhibition of various biomarkers of alternative pathway activity
- **These results suggest that iptacopan may reduce proteinuria and stabilize renal function in patients with IgAN and support further evaluation of iptacopan in the ongoing Phase 3 APPLAUSE-IgAN trial (NCT04578834; currently recruiting)**

BID, twice daily; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; UPCR, urine protein-to-creatinine ratio