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Efficacy and safety of iptacopan in IgA nephropathy: Results of a randomized double-blind placebo-controlled Phase 2 study at 6 months

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On behalf of the Iptacopan IgAN Program Steering Committee

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Disclosure

- Research funding: Reata Pharmaceuticals, Travere Therapeutics (Retrophin), Achillion Pharmaceuticals, Pfizer Pharmaceuticals, Calliditas Therapeutics (Pharmalinks), Otsuka Pharmaceuticals (Visterra)
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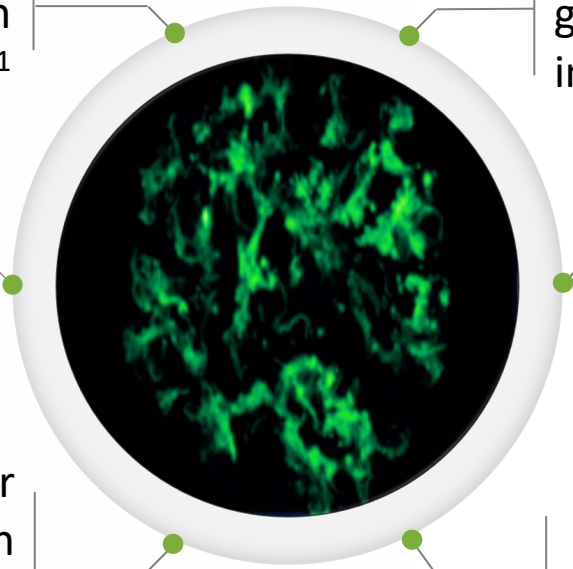
Introduction

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

Most common form of primary glomerulonephritis worldwide with a global incidence of **20–40/million/year**[6-8]

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



15–40% of patients develop **worsening kidney function** and progress to **kidney failure** within 10–20 years of diagnosis[9]

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

Supportive care (with max. tolerated ACEi/ARB) remains the basis of management of IgAN[10–12]

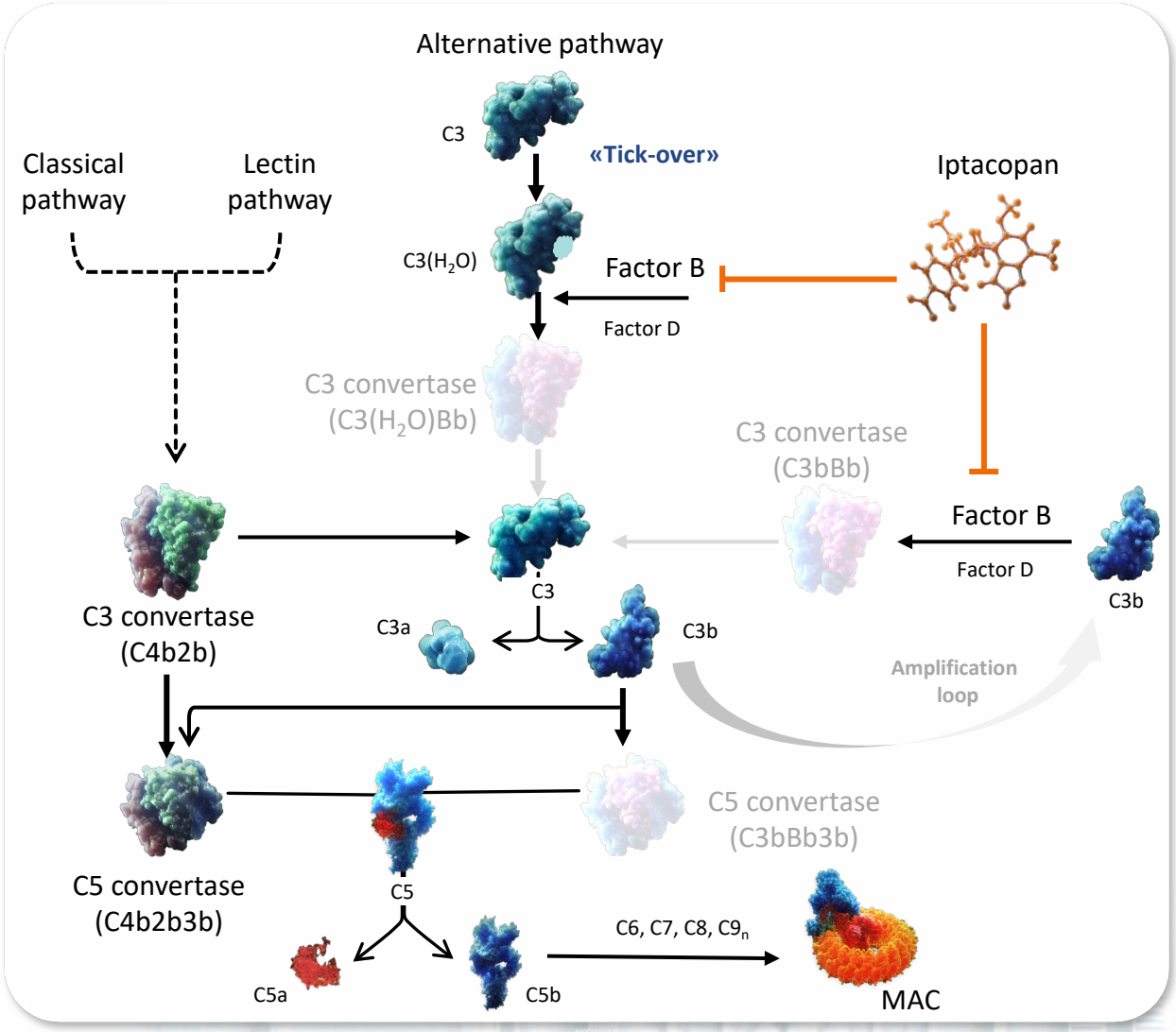
There is a need for effective and well-tolerated targeted therapies for IgAN that slow or prevent progression to kidney failure[9,10]

ACEi, angiotensin-converting enzyme inhibitor; AP, alternative pathway; ARB, angiotensin receptor blocker; IgA, immunoglobulin A; CFHR, complement factor H related protein; CKD, chronic kidney disease; IgAN, immunoglobulin A nephropathy; LP, lectin pathway; max., maximally.

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; 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. Rizk DV, et al. Front Immunol 2019;10:504. 8. Onda K, et al. J Clin Lab Anal 2007;21:77-84. 9. Xie J, et al. PLoS One 2012;7:e38904; 10. Reich HN, et al. J Am Soc Nephrol 2007;18:3177–3183; 11. Gutiérrez E, et al. Nephron 2020;144:555–571; 12. Rovin BH, et al. Kidney Int. 2021;100:753–779.

Iptacopan in IgAN: Scientific rationale

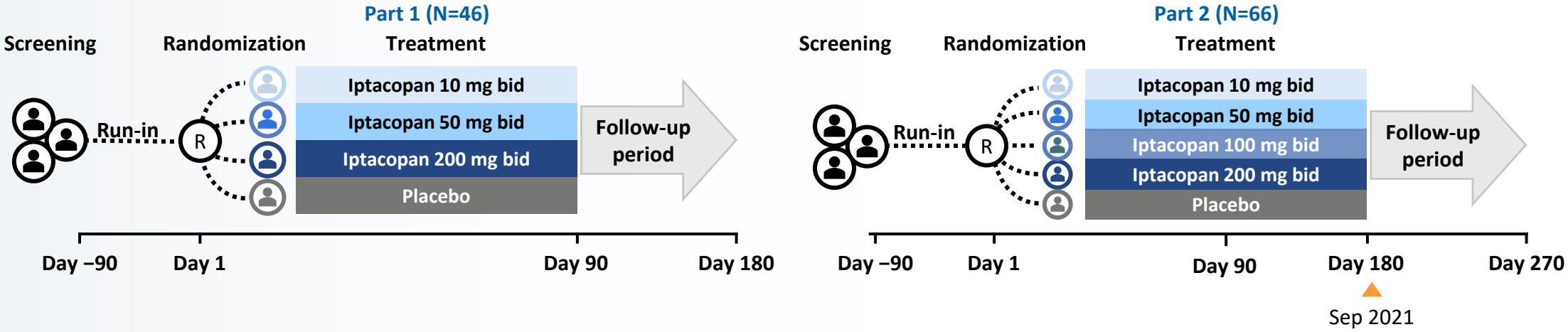
- **Iptacopan (LNP023)** is an oral, first-in-class, highly potent, selective small-molecule **inhibitor of factor B (FB)**[1]
- Given the contribution of a **dysregulated AP** in the **pathogenesis of IgAN**, inhibition of AP with iptacopan may provide an attractive therapeutic strategy to slow the disease progression[2]
- Primary results of the **Phase 2 study** of iptacopan in IgAN were presented at 58th ERA-EDTA Congress 2021 as late-breaking clinical trial
  - Treatment with iptacopan resulted in a significant dose-dependent reduction in proteinuria with 200 mg bid dose yielding a **23% reduction in UPCR (24 h) versus placebo at 3 months**[2]



AP, alternative pathway; bid, twice daily; FB, factor B; h, hour; IgAN, immunoglobulin A nephropathy; MAC, membrane attack complex; UPCR, urine protein-to-creatinine ratio.

1. Schubart A, et al. Proc Natl Acad Sci U S A 2019;116:7926–7931; 2. Barratt J, et al. Late breaking clinical trial presentation at 58th ERA-EDTA Congress, Fully Virtual, June 5–8, 2021.

Iptacopan in IgAN: Phase 2 study design



Study design	• Randomized, double-blind, dose-ranging, parallel-group adaptive design Phase 2 study (NCT03373461)
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
Patient population	• Adult IgAN patients (N=112) with UPCR of ≥0.8 g/g or proteinuria of ≥0.75 g/24 h at screening and at the end of the run-in period and eGFR of ≥30 mL/min/1.73 m^2 despite optimal ACEi or ARB therapy

In study Parts 1 & 2, 46 and 66 patients, respectively, were randomized; 58 patients completed 6 months of treatment in Part 2

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; bid, twice daily; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; R, randomization; UPCR, urine protein-to-creatinine ratio. 1. Barratt J, et al. Late breaking clinical trial presentation at 58th ERA-EDTA Congress, Fully Virtual, June 5–8, 2021; 2. https://clinicaltrials.gov/ct2/show/NCT03373461. Accessed Dec 15, 2021.

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 pneumoniae*[#], and *Haemophilus influenzae*[#]

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. 1. Barratt J, et al. Late breaking clinical trial presentation at 58th ERA-EDTA Congress, Fully Virtual, June 5–8, 2021.

Demographic and baseline characteristics

	Overall study cohort (Part 1 + Part 2)					Part 2				
	Iptacopan					Iptacopan				
	10 mg bid N=20	50 mg bid N=19	100 mg bid N=22	200 mg bid N=26	Placebo N=25	10 mg bid N=11	50 mg bid N=11	100 mg bid N=22	200 mg bid N=11	Placebo N=11
Age, years	39.2 (12.4)	36.6 (8.4)	36.0 (13.2)	42.5 (15.8)	39.4 (11.0)	42.6 (13.1)	39.2 (7.0)	36.0 (13.2)	36.7 (16.1)	39.4 (11.8)
Male	45%	68%	50%	58%	72%	45%	64%	50%	36%	55%
Asian ethnicity	45%	47%	55%	46%	44%	55%	55%	55%	55%	55%
BMI, kg/m^2	26.3 (5.5)	25.8 (4.4)	26.1 (4.6)	25.8 (4.4)	25.4 (3.7)	25.5 (4.8)	25.9 (4.4)	26.1 (4.6)	24.1 (4.3)	24.8 (4.0)
UPCR, g/mol*	214.1 (122.3)	188.2 (90.4)	203.4 (98.3)	151.0 (109.5)	146.6 (61.6)	221.4 (134.5)	170.1 (77.9)	203.4 (98.3)	169.7 (160.8)	158.4 (63.1)
UPCR ≥200 g/mol	45%	47%	32%	15%	20%	45%	45%	32%	9%	27%
eGFR, mL/min/1.73 m^2	66. (28.5)	53.8 (22.7)	67.0 (31.8)	57.9 (28.9)	65.7 (32.6	65.5 (25.1)	53.0 (23.2)	67.0 (31.8)	75.7 (32.2)	69.6 (38.3)
SBP, mmHg	134.4 (11.7)	122.6 (12.2)	125 (11.3)	125.7 (11.7)	125.5 (11.4)	129.0 (8.5)	115.3 (9.6)	125.0 (11.3)	122.7 (15.3)	118.7 (12.9)

Treatment groups were well-balanced in terms of demographics and baseline characteristics; In Part 2, iptacopan 200 mg bid arm had fewer patients with baseline UPCR ≥200 g/mol and higher baseline eGFR levels

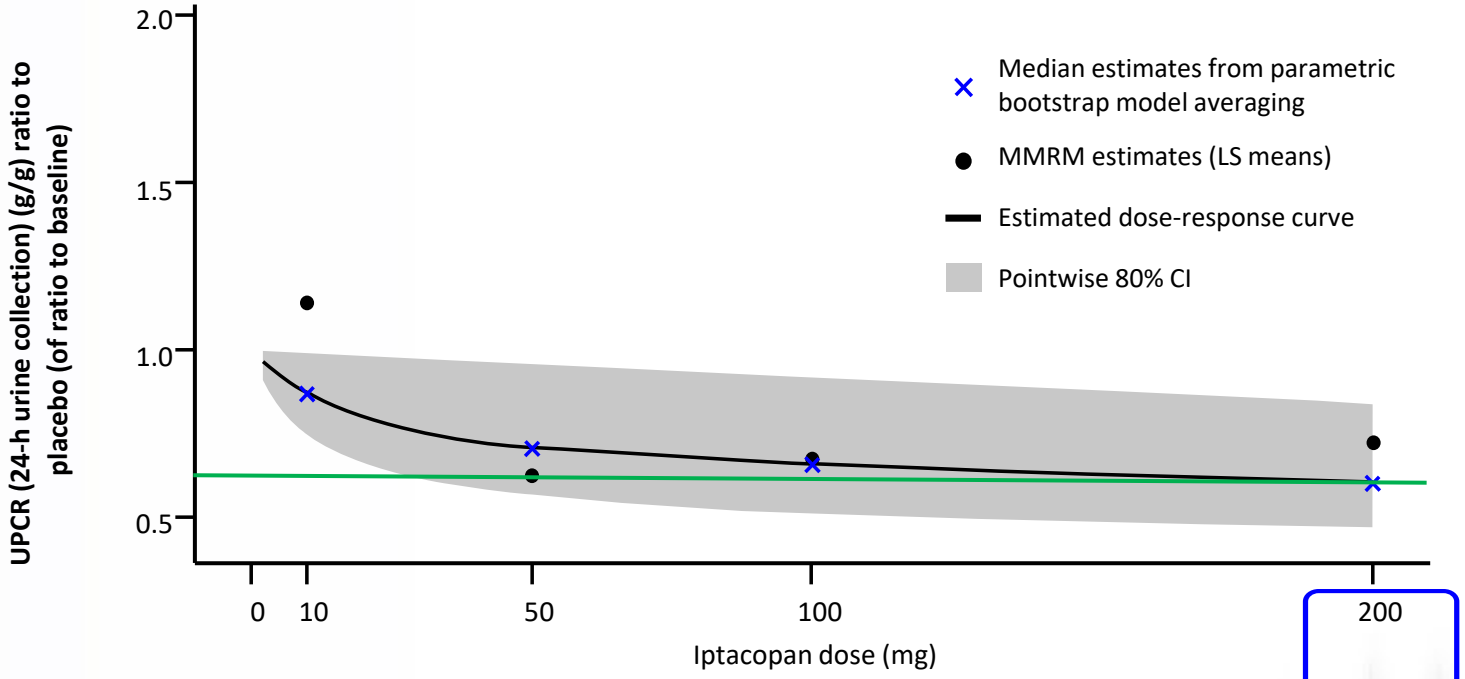
All values are mean (SD), unless specified. All baseline measurements were considered to be the last measurement prior to initiation of the study treatment.
*UPCR from 24-hour urine collection.
bid, twice daily; BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SD, standard deviation; UPCR, urine protein to creatinine ratio.

Proteinuria continued to decrease between 3 and 6 months

- **UPCR continued to decrease** between 3 and 6 months in the higher-dosed iptacopan arms (MCP-mod estimate for 200 mg bid arm 0.66; 80% CI: 0.48–1.03)
  - The wider CI reflects the small amount of 6 month data (available for Part 2 patients only)

- A *post hoc* analysis of pooled data from Parts 1 & 2 indicated that in iptacopan 200 mg bid arm **UPCR fell by 40%** (using MCP-mod model) to **28%** (using MMRM model) **from baseline at 6 months** versus placebo

Estimated UPCR reduction (placebo-corrected) and dose response relationship at 6 months*



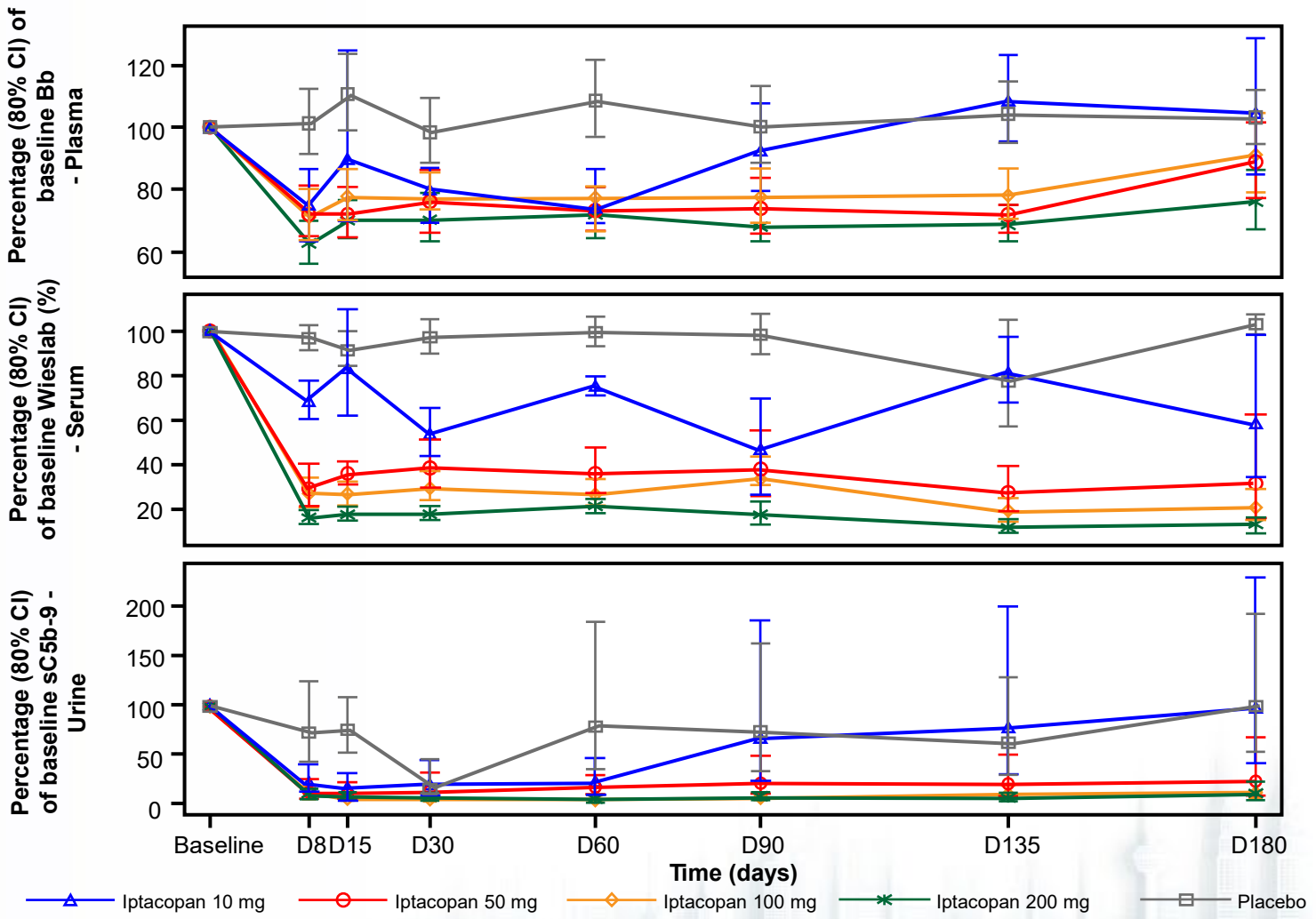
	0	10	50	100	200
MCP-mod estimate (80% CI)		0.87 (0.75, 0.99)	0.71 (0.57, 0.96)	0.66 (0.51, 0.92)	0.60 (0.47, 0.84)
MMRM estimate (80% CI)		1.14 (0.83, 1.57)	0.62 (0.45, 0.85)	0.67 (0.50, 0.90)	0.72 (0.54, 0.97)

**Post hoc* analysis of pooled data from Part 1 and Part 2

CI, confidence interval; h, hour; LS, least squares; MCP-mod, multiple comparison procedure – modeling; MMRM, mixed model for repeated measures; UPCR, urine protein-to-creatinine ratio..

Sustained inhibition of AP through 6 months of iptacopan treatment

- **Sustained inhibition of AP biomarkers**, including plasma Bb and serum Wieslab, through 6 months was observed with all doses of iptacopan above 10 mg bid
  - A **dose dependent AP inhibition** as measured by **Wieslab activity** was observed, with **near complete inhibition at 200 mg bid** dose
- **Urinary sC5b-9,** reflective of terminal pathway activation, reduced through 6 months
- These findings are **consistent with the MoA** of iptacopan



All assessments were pre-dose;
Data included here is for patients in Part 2 who received 6 months of treatment (N=60)

AP, alternative pathway; bid, twice daily; CI, confidence interval; D, day; MMRM, mixed model for repeated measures; MoA, mechanism of action.

Iptacopan was well tolerated

- Overall AEs: 77 (68.8%) patients
- Most common AEs: headache, back pain, diarrhea, nasopharyngitis, and vomiting
- Most AEs were of **mild or moderate** intensity
- There was no marked dose- or treatment-related difference in the rate of AEs between the treatment arms
- Iptacopan was well tolerated with **no deaths, no SAEs suspected to be treatment-related, and no serious infections** caused by encapsulated bacteria

	Iptacopan				Placebo
	10 mg bid N=20	50 mg bid N=19	100 mg bid N=22	200 mg bid N=26	N=25
≥1 AE*,	14 (70.0)	16 (84.2)	15 (68.2)	14 (53.8)	18 (72.0)
Mild	12 (60.0)	15 (78.9)	15 (68.2)	13 (50.0)	17 (68.0)
Moderate	4 (20.0)	2 (10.5)	2 (9.1)	3 (11.5)	7 (28.0)
Severe	0	1 (5.3)	0	0	0
Serious AEs	0	1 (5.3)	0	0	1 (4.0)
AEs leading to treatment discontinuation	0	1 (5.3)	0	0	2 (8.0)
AEs related to study drug	5 (25.0)	5 (26.3)	7 (31.8)	2 (7.7)	5 (20.0)
Study-drug–related AEs leading to treatment discontinuation	0	0	0	0	0

Data presented are number of patients n (%);
*A patient with an AE of multiple intensities is counted only once here

AE, adverse event; bid, twice daily; SAE, serious adverse event.

Conclusions

- Treatment with iptacopan resulted in significant and clinically meaningful reduction in proteinuria evident at 3 months (as observed in the previous analysis); proteinuria **continued to reduce through 6 months** in patients with IgAN
- **Strong inhibition** of biomarkers of **AP activation** and **sMAC formation** was also **sustained through 6 months** with all doses above iptacopan 10 mg bid
  - A dose dependent inhibition of AP (as assayed by Wieslab activity) was also observed
- Iptacopan was well tolerated with no serious infections caused by encapsulated bacteria, **no study-drug related AEs leading to discontinuation, no SAEs suspected to be treatment-related, and no deaths**
- These data further strengthen the results of primary analysis at 3 months[1] and support further evaluation of iptacopan (oral, FB inhibitor) in the **currently recruiting** Phase 3 **APPLAUSE-IgAN trial** (NCT04578834)

AP, alternative pathway; FB, factor B; IgAN, immunoglobulin A nephropathy; SAEs, serious adverse events; sMAC, soluble membrane attack complex.

1. Barratt J, et al. Late breaking clinical trial presentation at 58th ERA-EDTA Congress, Fully Virtual, June 5–8, 2021.