Effect of Iptacopan on Proteinuria and Complement Biomarkers Over Time in IgA Nephropathy

Brad H. Rovin,[1] Jonathan Barratt,[2,3] Hong Zhang,[4] Dana V. Rizk,[5] Naoki Kashihara,[6] Bart D. Maes,[7] Hernán Trimarchi,[8] Ben Sprangers,[9] Matthias Meier,[10] Dmitrij Kollins,[10] Annabel R. Magirr,[10] Guido Junge,[11] Vlado Perkovic[12]

[1]The Ohio State University Wexner Medical Centre, Columbus, OH, United States; [2]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [3]University of Leicester Department of Cardiovascular Sciences, Leicester, United Kingdom; [4]Peking University First Hospital Department of Nephrology Renal Division, Beijing, China; [5]The University of Alabama at Birmingham School of Medicine, Birmingham, AL, United States; [6]Kawasaki Ika Daigaku Jinzo Koketsuatsu Naikagaku Kyoshitsu, Okayama, Japan; [7]AZ Delta vzw, Roeselare, West-Vlaanderen, Belgium; [8]Hospital Britanico de Buenos Aires, Buenos Aires, Federal District, Argentina; [9]Katholieke Universitet Leuven Universitaire Ziekenhuizen Leuven Campus Gasthuisberg, Leuven, Flanders, Belgium; [10]Novartis Pharma AG, Basel, Switzerland; [11]Novartis Institutes for BioMedical Research, Basel Department of Translational Medicine, Basel, Switzerland; [12]University of New South Wales, Sydney, NSW, Australia

This study was sponsored by Novartis Pharma AG

FR-OR59 | Presented at the ASN Kidney Week Congress 2022 | Nov 3–6 | Orlando, FL, US

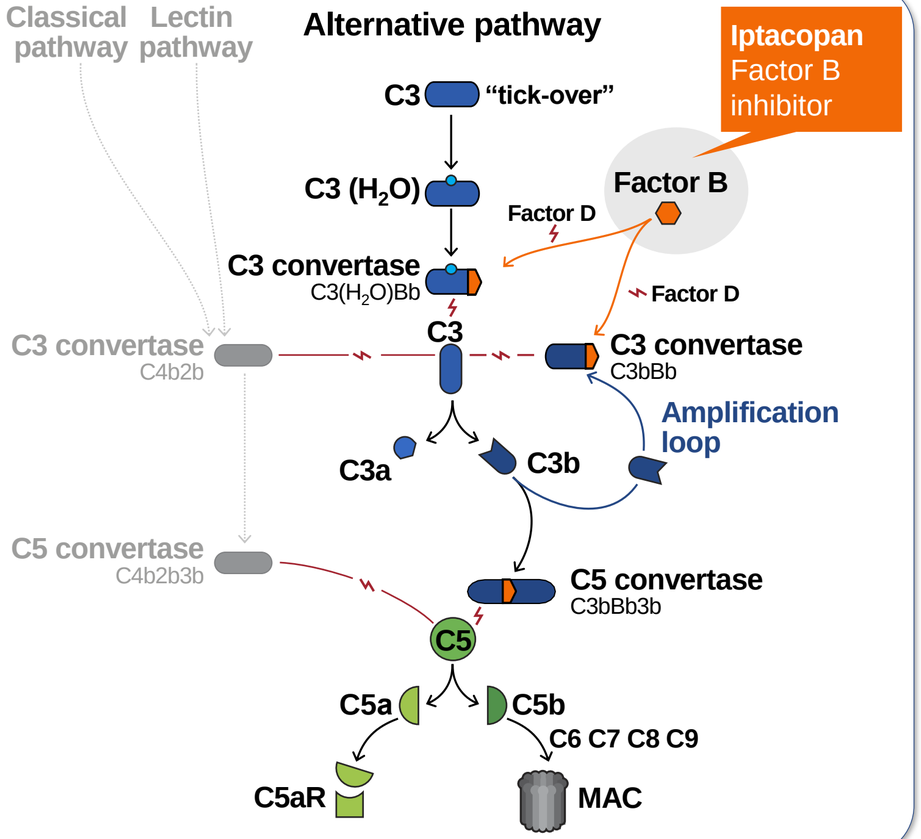
Scan the QR code to view a copy of this presentation

Disclosures and acknowledgements

- Brad Rovin has received research funding from the National Institutes of Health and advisory fees from Alexion, AstraZeneca, Aurinia Pharmaceuticals, Biocryst, Biogen, Bristol Myers Squibb, Calliditas Therapeutics, Chemocentryx, Corrona, EMD Serono/Merck, Exagen, Galapagos, Genentech, Horizon, Human Genome Sciences (GlaxoSmithKline), Idorsia, Janssen Pharmaceuticals, MedImmune, MorphoSys, Novartis, Omeros, Otsuka, Resonance, Retrophin, RILITE Foundation, Roche, and Vistera
- This study was sponsored by Novartis Pharma AG
- The authors would like to thank Julie Milovejic and Olympia Papachristofi for their valuable contributions towards data analysis and interpretation
- Medical writing and editorial support was provided by Maria Alfaradhi, PhD, funded by Novartis Pharma AG

Iptacopan is an oral, highly potent, selective alternative complement pathway inhibitor

- IgA nephropathy is the most common form of primary glomerulonephritis worldwide with a global incidence of ~25 adults/million/year[1,2]
- The alternative complement pathway (AP) plays a key role in the pathophysiology of IgAN[1]
- Iptacopan (LNP023) is an oral, first-in-class, highly potent proximal complement inhibitor that specifically binds to factor B and inhibits the AP[3]
- In a Phase 2 study (NCT03373461), iptacopan treatment led to a dose-dependent reduction in proteinuria and inhibition of the AP in patients with IgAN[4,5]



References

1. Rizk DV, et al. Front. Immunol. 2019;10:504; 2. McGrogan A, et al. Nephrol Dial Transplant. 2011;26:414–30; 3. Schubart A, et al. Proc Natl Acad Sci U S A. 2019;116:7926–31; 4. Barratt J, et al. S0.1 Oral presentation at 58th ERA-EDTA Congress; June 6, 2021;https://www.era-online.org/en/virtual-meeting/#!resources/interim-analysis-of-a-phase-2-dose-ranging-study-to-investigate-the-efficacy-and-safety-of-iptacopan-in-primary-iga-nephropathy-20ec3f83-fd34-441e-8745-44587bda74da (Last accessed Jul 27, 2022); 5. Barratt J, et al. Kidney Int Rep. 2022;7(Suppl S236): abst. POS-546.

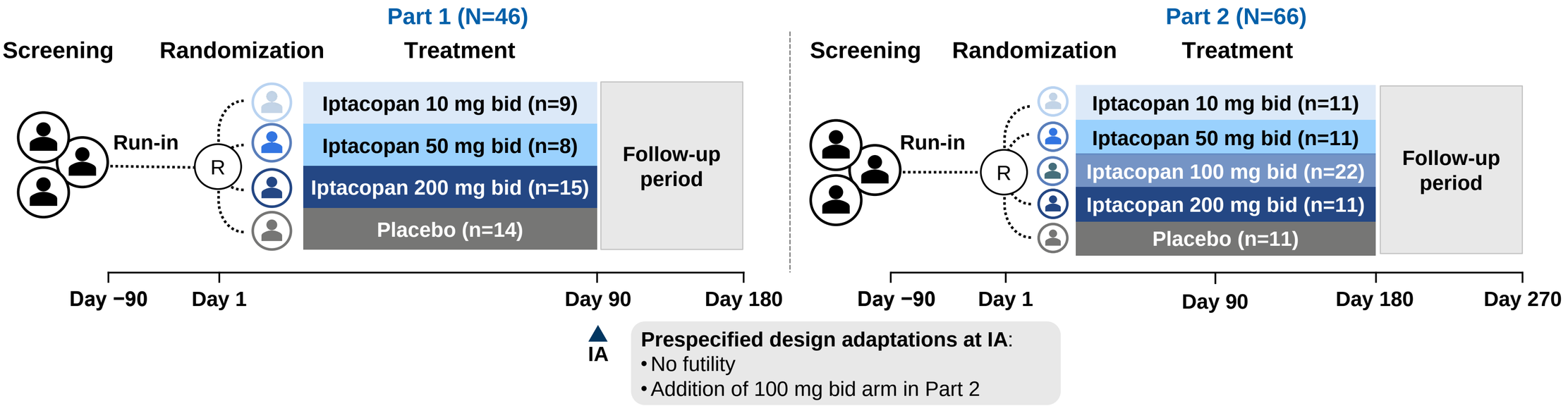
Abbreviations

AP, alternative complement pathway; C, complement; IgAN, IgA nephropathy; MAC, membrane attack complex.

KIDNEY WEEK 2022

A Phase 2, adaptive, seamless, randomized, double-blind, placebo-controlled study in IgAN

- A two-part study (NCT03373461) where patients with biopsy-confirmed IgAN were randomized to one of four iptacopan doses or placebo for either a 3-month (Part 1; N=46) or 6-month (Part 2; N=66) treatment period



Patients

- Age ≥18 years with biopsy-verified IgAN within the prior 3 years
- UPCR ≥0.8 g/g or proteinuria ≥0.75 g/24 h at the end of run-in period, and eGFR of ≥30 mL/min/1.73 m^2
- On maximally tolerated dose of ACE inhibitor/ARB for at least 3 months

Abbreviations

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; bid, twice daily; eGFR, estimated glomerular filtration rate; IA, interim analysis; IgAN, IgA nephropathy; R, randomization; UPCR, urine protein-to-creatinine ratio.

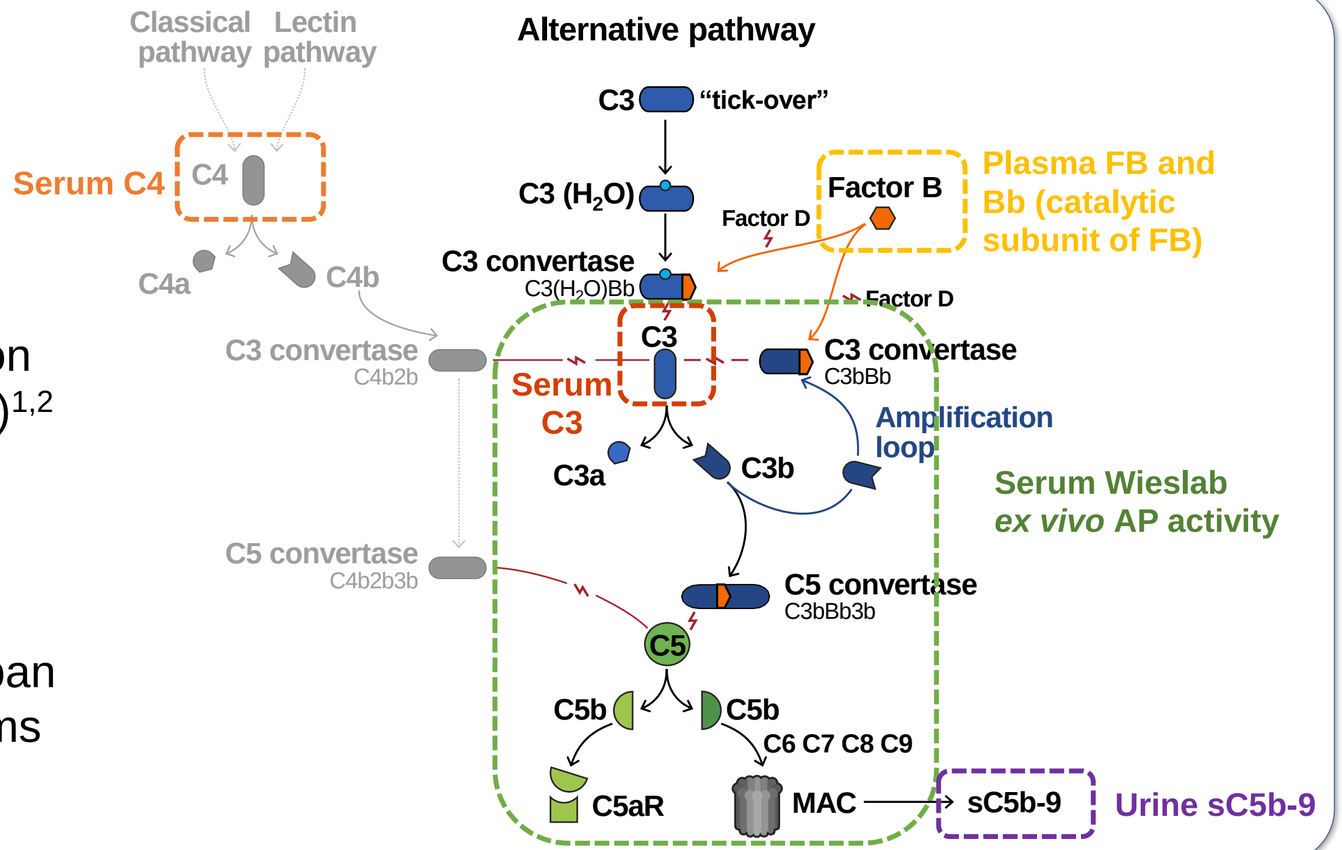
Analyses presented

- We compared the effect of iptacopan vs placebo at the 3-month and 6-month timepoints with respect to:

  1. Percentage change from baseline in UPCR based on 24-hour urine collection (assessed by the MCP-Mod procedure)[1,2]

  2. Percentage change from baseline in biomarkers of complement activity

- Here, we present the results of the iptacopan 200 mg bid (n=26) and placebo (n=25) arms from Parts 1 and 2 combined



References

1. Bretz F, Pinheiro JC, Branson M. Biometrics. 2005;61(3):738–48;
2. Pinheiro J, et al. Stat Med. 2014;33(10):1646–61.

Abbreviations

bid, twice daily; C3, complement 3; C4, complement 4; FB, factor B; MCP-Mod, Multiple Comparisons Procedure – Modelling; sC5b-9, soluble membrane attack complex; UPCR, urine protein-to-creatinine ratio.

Demographics and baseline characteristics were mostly balanced between groups (1/2)

	Iptacopan 200 mg bid N=26	Placebo N=25
Age, years	42.5 (15.8)	39.4 (11.0)
Male (%)	58%	72%
Asian ethnicity (%)	46%	44%
UPCR, g/g*	1.3 (1.0)	1.3 (0.6)
UPCR <200 g/mol [<1.77 g/g] (%)	85%	80%
eGFR, mL/min/1.73 m^2	57.9 (28.9)	65.7 (32.6)
IgAN Oxford Classification/MEST-C score†	n=24	n=22
Mesangial proliferation (M1), %	33%	50%
Endocapillary hypercellularity (E1), %	46%	36%
Segmental glomerulosclerosis (S1), %	71%	82%
Tubular atrophy/interstitial fibrosis (T1/2), %	25%	36%
Cellular/fibrocellular crescents (C1/2), %	33%	45%

Combined Part 1 and 2 data are presented.
Data are mean (SD) unless otherwise specified.
*UPCR sampled from a 24-hour urine collection at baseline; †MEST-C scoring was performed centrally based on scans provided by study sites. N=number of all patients included in the analysis; n=number of patients with non-missing measurements.

Abbreviations

bid, twice daily; eGFR, estimated glomerular filtration rate; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

Demographics and baseline characteristics were mostly balanced between groups (2/2)

	Iptacopan 200 mg bid N=26	Placebo N=25
Complement pathway biomarkers		
Serum C3, g/L (*ref. range: 0.9–1.8*)[1]	1.3 (16.3)	1.3 (20.6)
Plasma FB, µg/mL (*ref. range: 340–450)*[2]	425.9 (32.8)	421.4 (21.4)
Plasma Bb, ng/mL (*ref. range: 446–3920; geomean 1426*)[3]	1973 (43.8)	1795 (29.4)
Plasma sC5b-9, ng/mL (*ref. range: 44.8–231; geomean 112.7*)[3]	144.0 (30.5)	131.1 (34.0)
Urine sC5b-9, pg/mL (*ref. range: 43.2–162.0*)[2]	2971 (427.7)	1887 (318.9)

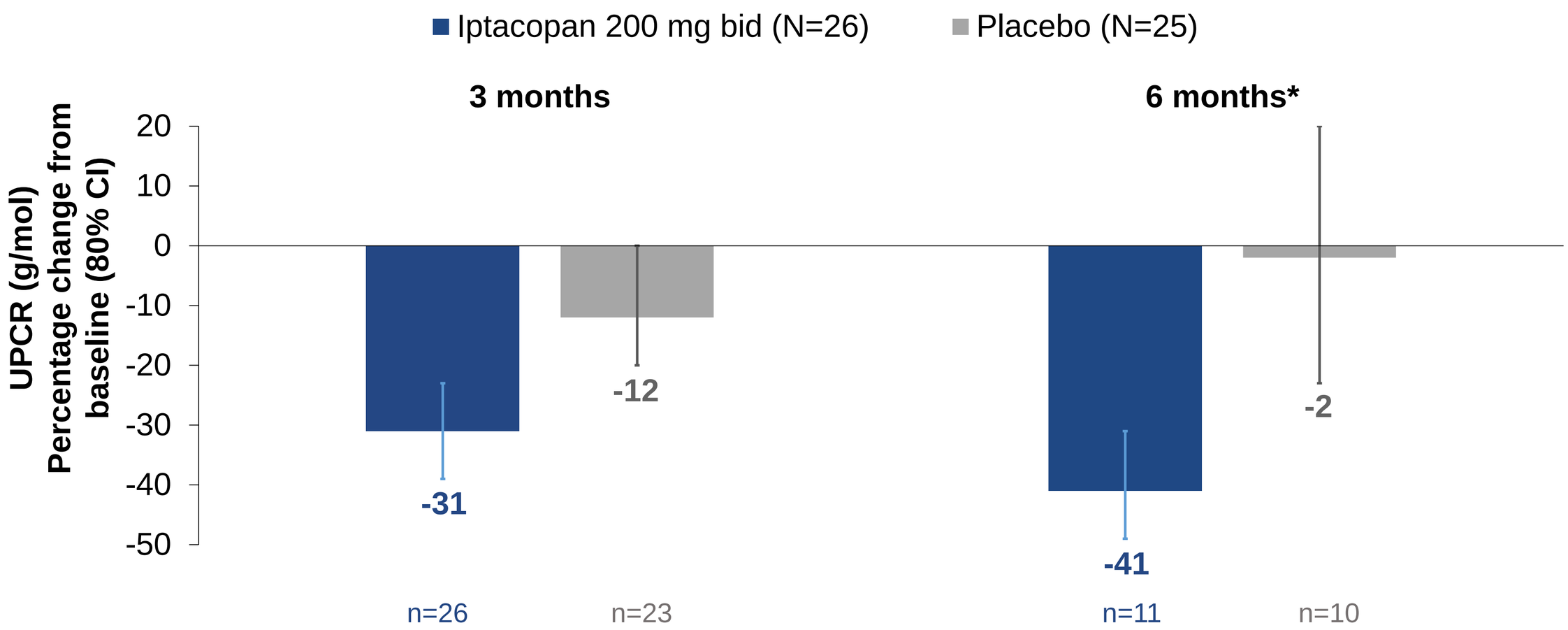
Data are geomean (geo-CV%).

1. Cobas® C3C-2 Tina-quant Complement Assay Information sheet 2017-08 V5.0; 2. Data on File. Based on n=6 healthy donors. Novartis; 3. Data on File. CLNP023X2101 Study. Novartis; Dec 01, 2017.

Abbreviations

bid, twice daily; C3, complement 3; FB, factor B; sC5b-9, soluble membrane attack complex.

Iptacopan reduced proteinuria at 3 months, which continued to decrease at 6 months



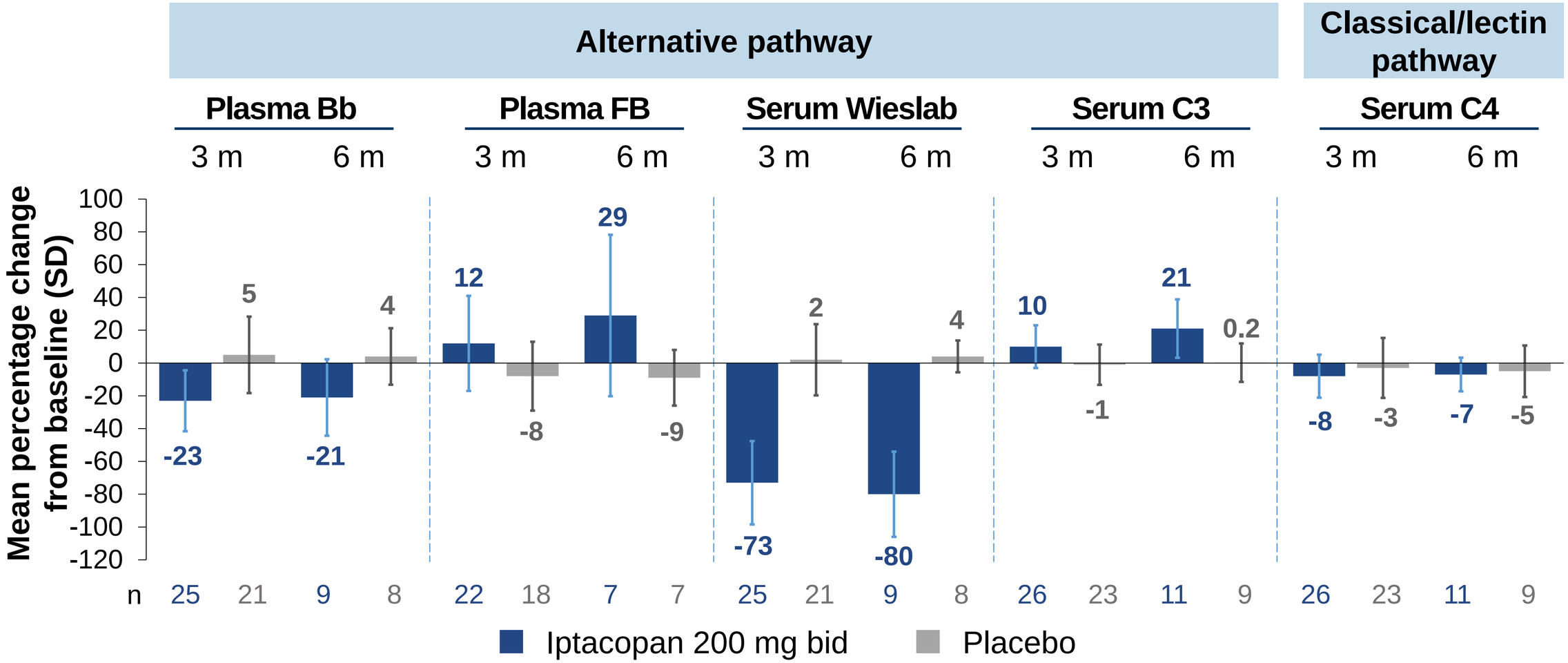
*Post-hoc analysis of data pooled from Part 1 and Part 2. Only 11 and 10 patients receiving iptacopan 200 mg bid and placebo, respectively, from Part 2 provided data for the 6-month timepoint.
N=number of all patients included in the analysis; n=number of patients with non-missing measurements at baseline and 3 and 6 months. UPCR from 24-hour urine collection.

Abbreviations

bid, twice daily; CI, confidence interval; UPCR, urine protein-to-creatinine ratio.

KIDNEY WEEK 2022

Changes in complement pathway biomarkers were consistent with sustained and selective AP inhibition



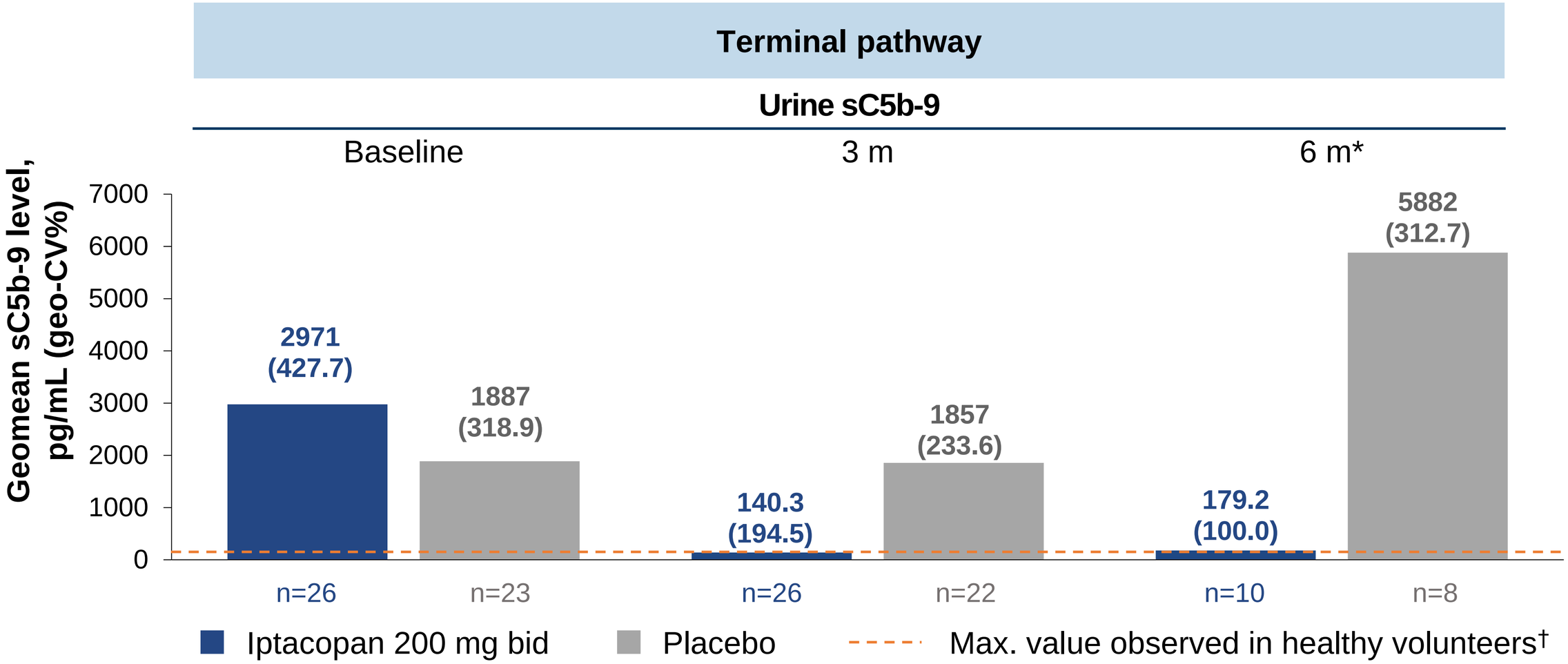
3-month analyses include data pooled from Part 1 and Part 2 (N=26 for iptacopan 200 mg bid and N=25 for placebo), while 6-month analyses include data from Part 2 only (N=11 for each group).
N=number of all patients included in the analysis; n=number of patients with non-missing measurements at each timepoint.

Abbreviations

bid, twice daily; C3, complement 3; C4, complement 4; FB, factor B; m, month; SD, standard deviation.

KIDNEY WEEK 2022

Iptacopan fully suppressed complement terminal pathway activity in the urine



*3-month analyses include data pooled from Part 1 and Part 2 (N=26 for iptacopan 200 mg bid and N=25 for placebo), while 6-month analyses include data from Part 2 only (N=11 for each group).
†Data on File. Based on n=6 healthy donors. Novartis.
N=number of all patients included in the analysis; n=number of patients with non-missing measurements at each timepoint.

Abbreviations

bid, twice daily; geo-CV, geometric coefficient of variation; m, month; sC5b-9, soluble membrane attack complex.

Conclusions

- In accordance with its mechanism of action, iptacopan 200 mg bid inhibited activation of the alternative complement pathway with a measurable decrease in Wieslab assay activity and near complete suppression of urine sC5b-9 to near the range observed in healthy volunteers, which was sustained after 6 months of treatment
- This resulted in clinically meaningful reductions in proteinuria in patients with IgAN after 3 and 6 months of treatment that are expected to translate to improved kidney outcomes in patients
  - Based on a meta analysis of 12 clinical trials, a 30% reduction in proteinuria suggests ≥90% probability of a treatment benefit on eGFR stabilization[1]
- The results from this Phase 2 study of iptacopan strengthen the therapeutic rationale for selective alternative pathway inhibitors such as iptacopan in IgAN and further support its evaluation in preventing renal function loss in the ongoing Phase 3 APPLAUSE-IgAN trial (NCT04578834; currently recruiting)

References

1. Inker LA, et al. Am J Kidney Dis. 2021;78(3):340–349.e1.

Abbreviations

bid, twice daily; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; sC5b-9, soluble membrane attack complex.