The World Congress of Nephrology (WCN) 2023
Bangkok, Thailand, March 30 – April 2, 2023

Abstract title:

Effect of iptacopan on proteinuria and complement biomarkers over time in IgA nephropathy

Abstract text:

Introduction: IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide. The alternative complement pathway (AP) plays a key role in the pathogenesis of IgAN. Iptacopan (LNP023) is an oral, first-in-class, highly potent proximal complement inhibitor that specifically binds factor B and inhibits the AP. In a Phase 2 study, iptacopan treatment led to a dose-dependent reduction in proteinuria and inhibition of the AP in patients with IgAN.

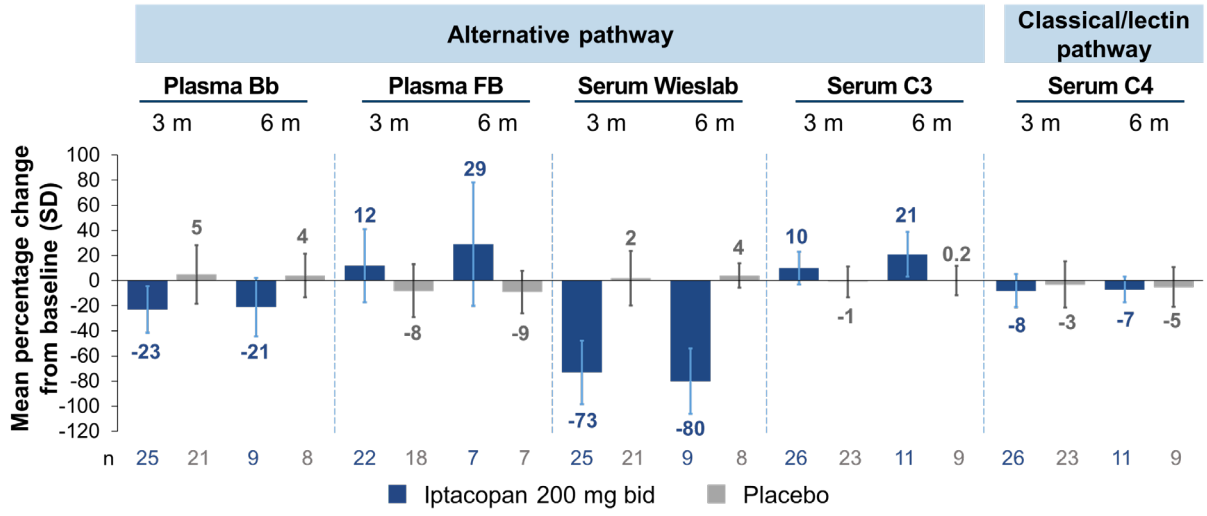
Methods: This parallel-group, adaptive design Phase 2 study (NCT03373461) randomized patients with biopsy-confirmed IgAN to one of four iptacopan doses (10, 50, 100, or 200 mg twice daily [bid]) or placebo bid for either a 3-month (Part 1; N=46) or 6-month (Part 2; N=66) treatment period. In this analysis, we report changes in proteinuria (ratio to baseline in urine protein-to-creatinine ratio [UPCR]), and biomarkers of complement activity (plasma Bb, FB, complement 3 [C3] and complement 4 [C4], serum Wieslab activity, and urine soluble complement 5b-9 [sC5b-9]) with iptacopan 200 mg bid (n=26) vs placebo (n=25) at 3 months (pooled Part 1 and 2 data) and 6 months (Part 2).

Results: UPCR decreased by 31% (80% CI: 23%, 39%) versus 12% (0%, 20%) from baseline to 3 months and by 41% (49%, 31%) versus 2% (-20%, 23%) from baseline to 6 months (post-hoc analysis of Part 1 and 2) in the iptacopan 200 mg bid arm versus the placebo arm, respectively. Iptacopan selectively inhibited the AP as demonstrated by changes from baseline in Wieslab activity, Bb, and FB levels, and small increases in C3 compared to baseline; C4 levels remained largely unchanged, indicating that iptacopan does not inhibit classical/lectin pathway (Figure 1A). Iptacopan suppressed complement terminal pathway activity in the urine, demonstrated by reduced urine sC5b-9 to near the range observed in healthy volunteers (Figure 1B). AP inhibition was sustained to 6 months of treatment (Figure 1A and 1B).

Conclusion: In accordance with its mechanism of action, iptacopan 200 mg bid inhibited activation of the AP and resulted in clinically meaningful reductions in proteinuria in patients with IgAN. The magnitude of reduction with iptacopan 200 mg bid is expected to translate to a reduced risk of chronic kidney disease progression. These results strengthen the therapeutic rationale for selective AP 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).

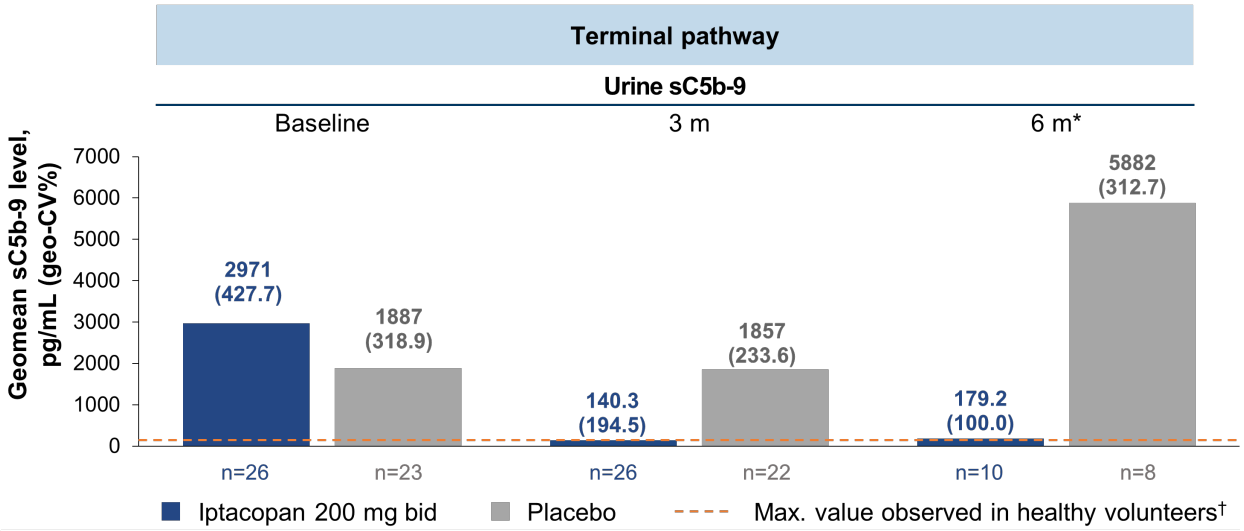
These data were previously presented at ASN Kidney Week 2022.

Figure 1A. Effect of iptacopan on biomarkers of complement activation



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

Figure 1B. Effect of iptacopan on urine sC5b-9



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

Key words: Phase 2, iptacopan, IgA nephropathy, complement, biomarkers

Authors: Jonathan Barratt,[1,2] Brad H. Rovin,[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] Guido Junge,[11] Julie Milojevic,[11] Olympia Papachristofi,[10] Vlado Perkovic[12]

Institutions:

[1]*University Hospitals of Leicester NHS Trust, Leicester, United Kingdom;*
[2]*University of Leicester Department of Cardiovascular Sciences, Leicester, United Kingdom;*
[3]*The Ohio State University Wexner Medical Centre, Columbus, OH, United States;*
[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*

The World Congress of Nephrology (WCN) 2023
Bangkok, Thailand, March 30 – April 2, 2023

Abstract topic: Chronic Kidney Disease, Hypertension, Diabetes and CVD – Other CKD

See complete list of topics here

Transparency declaration and ethics statement:

This study was conducted according to International Council for Harmonization E6 Guidelines for Good Clinical Practice that have their origin in the Declaration of Helsinki.

Declaration of funding and interests:

This analysis was funded by Novartis Pharma AG.

Professional medical writing assistance was provided by Maria Alfaradhi at Pharmaceuticals UK Limited, London, UK, funded by Novartis Pharma AG.

Jonathan Barratt: Research funding from Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Roche, Travere Therapeutics, and Visterra, Inc.; Consultancy fees from Alnylam, Astellas, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Roche, Travere Therapeutics, UCB, and Visterra, Inc.; Provided expert scientific advice to Alnylam, Astellas, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Roche, Travere Therapeutics, UCB, and Visterra, Inc.; is a member of Kidney Health Initiative; Lectured, chaired, or participated in symposia/panel discussions for Calliditas, Omeros, and Travere Therapeutics; **Brad Rovin**: 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; **Hong Zhang**: Consultation fees from and serves in the Steering Committee for Janssen, Novartis, Omeros, Calliditas, and Chinook; **Dana Rizk**: Research funding from Reata Pharmaceuticals, Travere Therapeutics (Retrophin), Achillion Pharmaceuticals, Pfizer Pharmaceuticals, Calliditas Therapeutics (Pharmalinks), Otsuka Pharmaceuticals (Visterra); Consultancy fees from Novartis, George Clinical, Otsuka Pharmaceuticals (Visterra), Calliditas Therapeutics (Pharmalinks), Angion; Ownership in Reliant Glycosciences LLC; **Naoki Kashihara**: personal fees from Daiichi Sankyo Co., Ltd; research funding from AstraZeneca, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, and Daiichi Sankyo Co., Ltd; **Bart Maes**: consultancy fees from Pharmalink AB; holds the following positions: National Leader ASCEND ND and D trial, GSK; National Leader Nefigard trial, Calliditas; National Leader, DUPLEX and PROTECT trial, Travere Therapeutics; and Steering Committee Member, Iptacopan IgAN trial, Novartis; **Hernán Trimarchi**: consultancy agreements with, and honoraria from Alexion, Calliditas, Chinook, Novartis, Sanofi Genzyme, Travere, and Visterra-Otsuka; **Ben Sprangers**: consultancy fees from AstraZeneca, Vifor Pharma, Boehringen, Janssen-Cilag; holds the following positions: National Leader Artemis Omeros; and Steering Committee Member, Iptacopan IgAN trial, Novartis; M-Place study Morphosys; **Matthias Meier, Dmitrij Kollins, Annabel Maggir**, **Julie Milojevic**, **Olympia Papachristofi**, and **Guido Junge** are employees and stockholders of Novartis; **Vlado Perkovic**: Advisory boards fees, steering committee roles, or scientific presentation fees from AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Chinook, Dimerix, Durect, Eli Lilly, Gilead,

GlaxoSmithKline, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, PharmaLink, Relypsa, Sanofi, Servier, Travere, Vifor, and Tricida.