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

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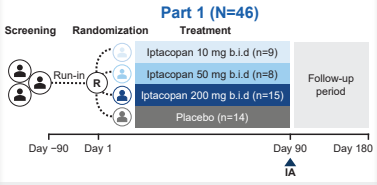
Introduction

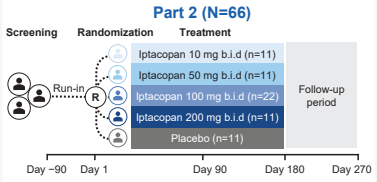
- IgA nephropathy is the most common form of primary glomerulonephritis, with a global incidence of ~25 adults/million/year[1,2]
- The alternative complement pathway (AP) plays a key role in the pathophysiology of IgAN[1]
- Iptacopan (LNP023) is an oral, first-in-class, highly potent proximal complement 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]
- The aim of this analysis was to evaluate the effect of iptacopan 200 mg b.i.d vs placebo on proteinuria reduction and changes in biomarkers of complement activation at 3- and 6-months

Methods

- 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



Prespecified design adaptations at IA: ● No futility ● Addition of 100 mg b.i.d arm in Part 2

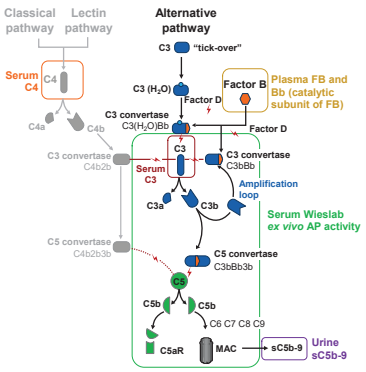


Patients

- Age ≥18 years with biopsy-confirmed IgAN within the prior 3 years
- UPCR ≥0.8 g/g or proteinuria ≥0.75 g/24 hour 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

Study analysis

- In this exploratory analysis, we compared the effect of iptacopan vs placebo at 3-and 6-month with respect to:
  - Percentage change from baseline in UPCR based on 24-hour urine collection (assessed by the MCP-Mod procedure)
  - Percentage change from baseline in biomarkers of complement activity

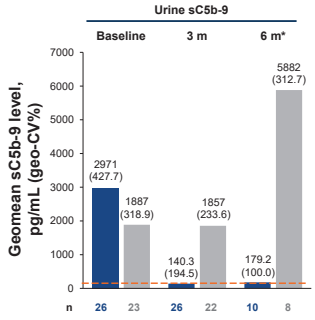


- Here, we present the results of the iptacopan 200 mg b.i.d (n=26) and placebo (n=25) arms from Parts 1 and 2 combined

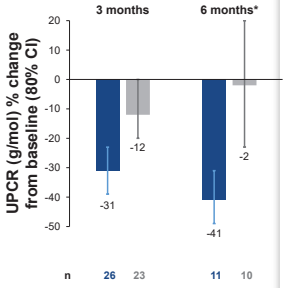
Conclusions

- In accordance with its mechanism of action, iptacopan 200 mg b.i.d inhibited activation of the alternative complement pathway as demonstrated by pronounced inhibition of Wieslab assay activity and urine sC5b-9 to near the range observed in healthy volunteers, which was sustained after 6 months of treatment
- Iptacopan treatment 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[6]
- 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)

Iptacopan suppressed complement terminal pathway activity in the urine



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

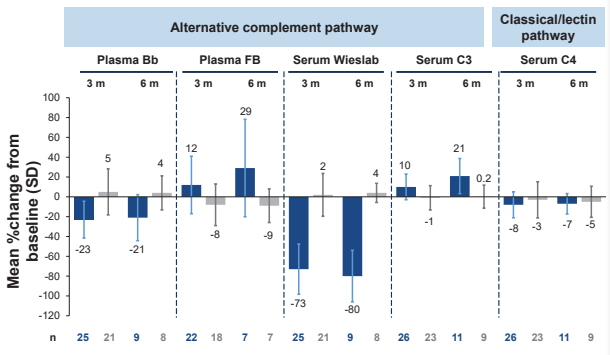


■ Iptacopan 200 mg b.i.d ■ Placebo -- Max. value observed in healthy volunteers†

*3-month analyses include data pooled from Part 1 and Part 2 (N=26 for iptacopan 200 mg b.i.d 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

*Post-hoc analysis of data pooled from Part 1 and Part 2. Only 11 and 10 patients receiving iptacopan 200 mg b.i.d and placebo respectively from Part 2 provided data for the 6-month timepoint

Changes in plasma/serum complement 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 b.i.d and N=25 for placebo), while 6-month analyses includes data from Part 2 only (N=11 for each group)

Results

Demographics and baseline characteristics were mostly balanced between groups

	Iptacopan 200 mg b.i.d 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%
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 mean (SD) and geomean (geo-CV%).for biomarkers;
†MEST-C scoring was performed centrally based on scans provided by study sites
[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

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Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AP, alternative complement pathway; b.i.d, twice daily; eGFR, estimated glomerular filtration rate; Geomean, geometric mean; IA, interim analysis; IgA nephropathy; m, months; MAC, membrane attack complex; UPCR, urine:protein creatinine ratio.

Funding

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Conflict of Interest

JB reports receiving consulting and speaker fees from Alnyam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dmerix, Galapagos, Novartis, Omeros, Travere Therapeutics, Vera Therapeutics, Visterra; Grant support from Argenx, Calliditas, Chinook, Galapagos, GSK, Novartis, Omeros, Travere Therapeutics, Visterra; being scientific/medical advisorto Alnylam, Astellas, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Roche, Travere Therapeutics, UCB, and Visterra, Inc.; is a member of Kidney Health Initiative; has lectured, chaired, or participated in symposia/panel discussions for Calliditas, Omeros, and Travere Therapeutics.

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