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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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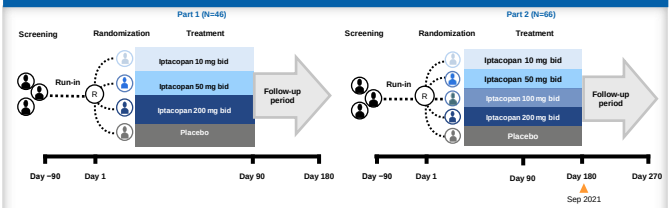
Introduction

- IgAN is the most common form of primary glomerulonephritis worldwide with a global incidence of **20–40/million/year**[1-3]
- 15–40% of patients with IgAN progress to **kidney failure** within 10–20 years of diagnosis[4]
- There is a need for effective and well-tolerated targeted therapies for IgAN that slow or prevent progression to kidney failure[4,5] as supportive care (with RAS inhibition) remains the basis of management
- **Iptacopan (LNP023)** is an oral, first-in-class, highly potent, selective small-molecule **inhibitor of complement factor B (FB)**[6]
- Since activation of **AP** plays a key role in the **pathogenesis of IgAN**, inhibition of AP with iptacopan may provide an attractive therapeutic strategy to slow the disease progression[7]
- Primary results of the **Phase 2 study** of iptacopan in IgAN showed 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**[7]

Study Design[6,7]



Primary objective	To evaluate the dose-response relationship of iptacopan on the reduction in proteinuria versus placebo after 90 days of treatment
Secondary objectives	Effect of iptacopan on eGFR, biomarkers reflecting activity of the alternative complement pathway and safety and tolerability of iptacopan
Patient population	Adult IgAN patients (N=112) with UPCR of ≥0.8 g/g (≥90 g/mol) 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 m² despite optimal ACEi or ARB therapy

Demographic and baseline characteristics

	Overall study cohort (Part 1 + Part 2)					Part 2				
	Iptacopan				Placebo N=25	Iptacopan				Placebo N=11
	10 mg bid N=20	50 mg bid N=19	100 mg bid N=22	200 mg bid N=26		10 mg bid N=11	50 mg bid N=11	100 mg bid N=22	200 mg bid 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/m²	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 m²	66.0 (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)

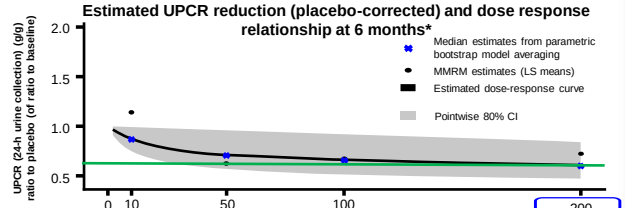
Treatment groups were well-balanced in terms of demographics and baseline characteristics; In Part 2, iptacopan 200 mg bid arm had fewer patients with baseline UPCR ≥200 g/mol and higher baseline eGFR levels

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.

Proteinuria continued to decrease between 3 and 6 months

- In a prespecified analysis, in patients who completed 6 months treatment in part 2 of the study, **UPCR continued to decrease** between 3 and 6 months in the higher-dosed iptacopan arms (data not shown)
- A post hoc analysis of pooled data from Parts 1 and 2 indicated that in iptacopan 200 mg bid arm **UPCR fell by 40%** (using MCP-mod model to model dose-response shape) **from baseline at 6 months** versus placebo (Figure)

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

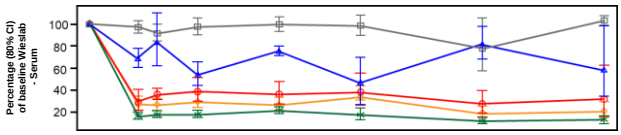


	0	10	50	100	200
MCP-mod estimate (80% CI)		0.87 (0.75, 0.99)	0.71 (0.57, 0.96)	0.66 (0.51, 0.92)	0.60 (0.47, 0.84)
MMRM estimate (80% CI)		1.14 (0.83, 1.57)	0.62 (0.45, 0.85)	0.67 (0.50, 0.90)	0.72 (0.54, 0.97)

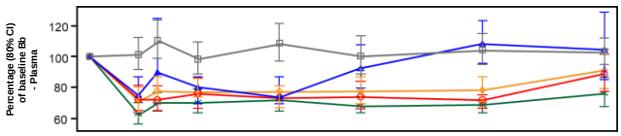
*Post hoc analysis of pooled data from Part 1 and Part 2

Sustained inhibition of AP through 6 months of iptacopan treatment

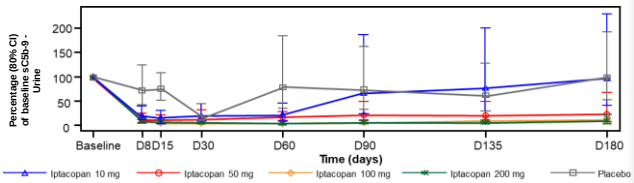
- **A dose dependent AP inhibition** as measured by **Wieslab activity** was observed, with **near complete inhibition at 200 mg bid** dose



- **Sustained reduction** in plasma Bb levels through 6 months with all doses of iptacopan above 10 mg bid



- **Urinary sC5b-9**, reflective of terminal pathway activation, reduced through 6 month with all doses of iptacopan above 10 mg bid



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

Iptacopan was well-tolerated

	Iptacopan				Placebo N=25
	10 mg bid N=20	50 mg bid N=19	100 mg bid N=22	200 mg bid N=26	
≥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)
Death	0	0	0	0	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

Conclusions

- Treatment with iptacopan resulted in significant and clinically meaningful reduction in proteinuria evident at 3 months[6] (by 23% with iptacopan 200 mg bid as observed in the previous analysis); proteinuria **continued to decline through 6 months** (by 40% with iptacopan 200 mg bid) in patients with IgAN
- Consistent with the MoA of iptacopan, **strong inhibition** of biomarkers of **AP activation** and urinary **sC5b-9** was also **sustained through 6 months** with all doses of iptacopan above 10 mg bid
  - A dose dependent inhibition of AP (as measured by Wieslab activity) was also observed
- Iptacopan was **well tolerated** with no marked dose-dependent toxicity; most AEs were of **mild or moderate** intensity
- 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** were observed
- These data further strengthen the results of primary analysis at 3 months[6] and support evaluation of iptacopan (oral, complement FB inhibitor) in the **currently recruiting** Phase 3 **APPLAUSE-IgAN trial** (NCT04578834)

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Abbreviations
AE, adverse event; AP, alternative pathway; BMI, body mass index; bid, twice daily; CI, confidence interval; D, day; eGFR, estimated glomerular filtration rate; FB, factor B; h, hour; IgAN, immunoglobulin A nephropathy; LS, least squares; MCP-mod, multiple comparison procedure–modeling; MMRM, mixed model for repeated measures; MoA, mechanism of action; R, randomization; SBP, systolic blood pressure; SD, standard deviation; SAEs, serious adverse events; sMAC, soluble membrane attack complex; UPCR, urine protein-to-creatinine ratio

‡Disclosure
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