Update to the long-term safety and efficacy of iptacopan in C3G: 33-month extension study data from patients enrolled in a Phase 2 study

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KEY FINDINGS & CONCLUSIONS

- Iptacopan is an **oral, proximal complement inhibitor** that specifically **targets Factor B and inhibits the AP**
- Long-term treatment with iptacopan was associated **with sustained reduction in proteinuria in patients with C3G (Cohort A), and preservation of eGFR (Cohort A + B)**
- Iptacopan was **well-tolerated with no new safety findings over long-term use** in patients with C3G, including those with C3G recurrence post-transplantation despite broad triple immunosuppression (CNI, CS and MPA)
- The ongoing **Phase 3 APPEAR-C3G** study (NCT04817618) is evaluating the efficacy and safety of iptacopan in adult and adolescent patients with C3G

This study is sponsored by Novartis Pharma AG
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INTRODUCTION

- C3G is an **ultra-rare, chronic, and severe form of primary glomerulonephritis** with an annual incidence of 1–2 per million around the globe.[1] It is caused by overactivation of the alternative pathway (AP) of the complement system, leading to C3 deposition in the glomerulus and triggering kidney inflammation and glomerular injury[2–6]
- Iptacopan (LNP023; 200 mg twice-daily [b.i.d.]) is an **oral, proximal complement inhibitor** that **targets Factor B to selectively inhibit the AP** of the complement cascade[7,8]
- **Previously reported data**[9,10]

Phase 2 extension study (NCT03955445) 12-month data[9,10]

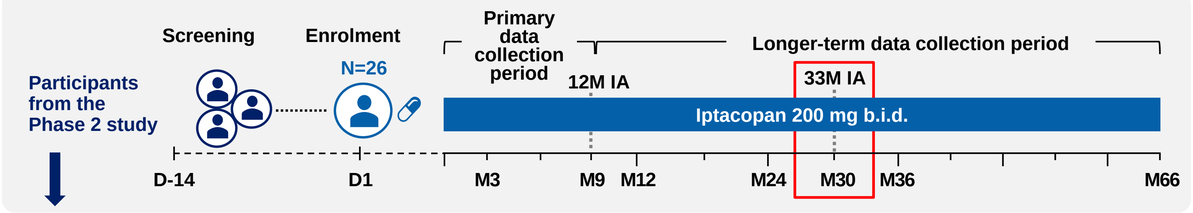
Following **12 months of treatment with iptacopan** in patients with C3G:
- **53% of native C3G patients met the composite renal endpoint*** (primary endpoint of the study [Cohort A])
- **Proteinuria reduction** (57% [p<0.0001], Cohort A)
- **Estimated glomerular filtration rate (eGFR) improvement** (by +6.83 mL/min/1.73m^2 [p=0.0174], Cohort A) from baseline
- **Increase in serum C3 levels** by 255% (p<0.0001), Cohort A

- Here we present further long-term efficacy data up to **33 months of iptacopan treatment (200 mg b.i.d., NCT03955445)** from patients with C3G (Cohort A) and recurrent C3G post-kidney transplantation (Cohort B) and their long-term safety and tolerability data up to the cut-off date

*Composite renal endpoint: stable/improved eGFR (≤10% reduction from baseline); ≥50% reduction from baseline in UPCR, and ≥50% increase from baseline in serum C3 after 12 months of treatment.

METHODS

- **C3G Phase 2 open-label extension study design (NCT03955445)**



- Adults with biopsy-confirmed C3G disease (**Cohort A**) or C3G recurrence post-transplantation (**Cohort B**) received iptacopan 200 mg b.i.d. for at least 12 weeks in the Phase 2 study (NCT03832114) before entering the open label extension study (NCT03955445)
- The 33-month interim analysis (IA) for efficacy data included patients treated with iptacopan for 3 months in the Phase 2 study plus 30 months treatment in the extension study

- **Long-term efficacy** was assessed by a number of renal endpoints, including:
  - A 2-component composite renal endpoint (eGFR stability [≤10% reduction] and ≥50% proteinuria reduction)
  - Change in urine protein–creatinine ratio (UPCR), eGFR, serum C3
- **Long-term safety and tolerability** of iptacopan treatment were continually monitored

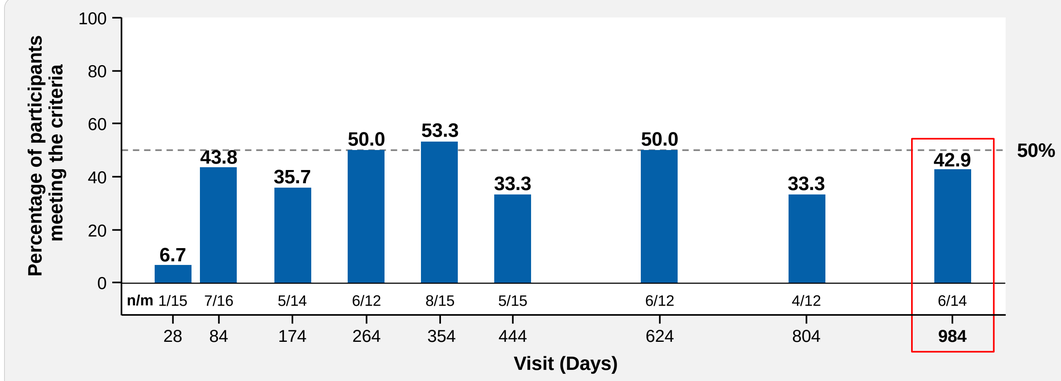
RESULTS

- Of 27 patients completing the Phase 2 study (NCT03832114):
  - 26 patients (16 Cohort A, 10 Cohort B) entered the extension study
  - **22 patients** (14 Cohort A, 8 Cohort B) **completed 33 months of follow-up**
- At baseline, median UPCR was within the normal range for Cohort B with C3G recurrence post-transplantation, but not for Cohort A with native kidney C3G

Baseline characteristics (NCT03955445)		Cohort A N=16	Cohort B N=10
Age (years)	Mean (SD)	26.1 (10.57)	35.9 (18.72)
	Median (Range)	22.0 (18–59)	32.5 (18–70)
Gender, n (%)	Male (%)	10 (62.5)	8 (80.0)
Race, n (%)	Caucasian (%)	16 (100)	9 (90.0)
	American Indian or Alaska Native (%)	–	1 (10.0)
eGFR (mL/min/1.73m^2)*	Mean (SD)	70.0 (35.05)	53.9 (17.14)
	Median (Range)	64.6 (28–134)	59.5 (27–74)
24 h UPCR (g/g)†	Mean (SD)	4.018 (2.143)	1.071 (1.6663)
	Median (Range)	3.457 (1.76–9.01)	0.162 (0.08–3.94)
FMV UPCR (g/g)†	Mean (SD)	3.613 (2.6934)	0.868 (1.6155)
	Median (Range)	2.863 (0.73–8.75)	0.079 (0.04–4.36)
Serum C3 (g/L)‡	Mean (SD)	0.312 (0.2224)	0.588 (0.2610)
	Median (Range)	0.238 (0.02–0.69)	0.550 (0.17–1.00)

*Normal eGFR: ≥60 mL/min/1.73m^2; †Normal UPCR: <200 mg/g; ‡Normal serum C3: 0.9–1.8 g/L

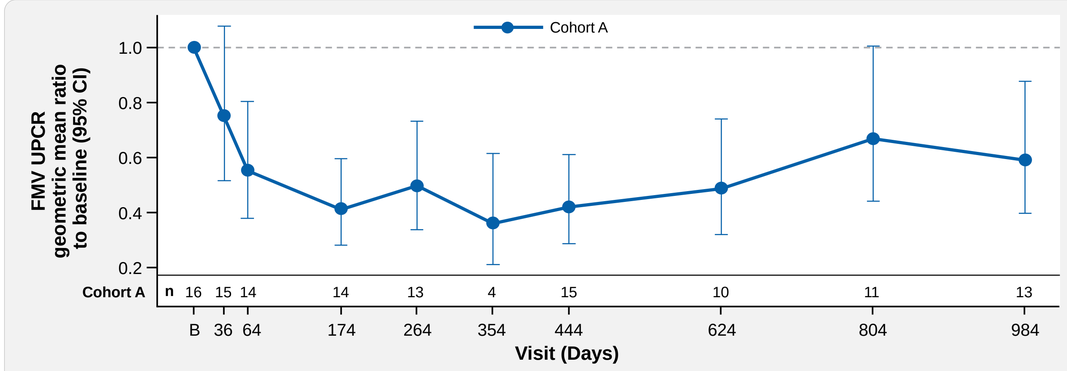
Figure 1. 42.9% (6/14) of patients (Cohort A) met the 2-component composite renal endpoint criteria i.e., eGFR stability [≤10% reduction] and ≥50% proteinuria reduction – at 33 months



m, number of participants at each time point; n, number of participants meeting the criteria at each time point

- Most participants in Cohort B had baseline UPCR in the normal range, therefore the composite endpoint was not assessed

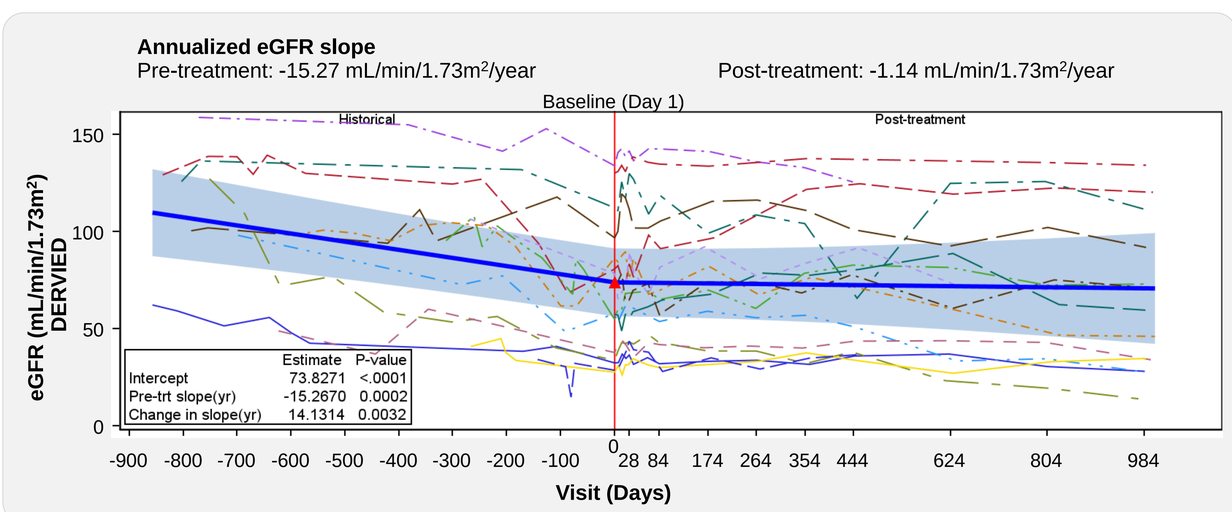
Figure 2. Proteinuria was reduced by 41% (p=0.0097) following 33 months of iptacopan treatment in Cohort A



n, number of participants with non-missing measurements

- Baseline proteinuria values (FMV UPCR) were within the normal range for most participants in Cohort B and remained so during iptacopan treatment

Figure 3. In Cohort A, the annualized eGFR slope (N=16) upon initiation of iptacopan was improved to -1.14 mL/min/1.73m^2/year representing a change in the eGFR trajectory of +14.13 mL/min/1.73m^2/year in annualized eGFR compared to the pre-treatment period (p=0.0032)



eGFR change from baseline at 33 months

- **Cohort A**: eGFR stabilized or improved in most patients (10/14) over time and change (adjusted arithmetic mean) from baseline at the 33-month time-point was -3.18 mL/min/1.73m^2
- **Cohort B**: eGFR change (adjusted arithmetic mean) from baseline at the 33-month follow-up was -6.34 mL/min/1.73m^2

Table 2. Overall cumulative summary of treatment-emergent adverse events (TEAEs*) (Safety analysis set)

	Cohort A; N=16		Cohort B; N=10		Overall; N=26	
	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)
Participants with at least one TEAE	122	15 (93.8)	105	10 (100)	227	25 (96.2)
Mild	110	15 (93.8)	66	10 (100)	176	25 (96.2)
Moderate	9	7 (43.8)	30	7 (70)	39	14 (53.8)
Severe	3	2 (12.5)	9	5 (50)	12	7 (26.9)
Serious TEAEs†	5	4 (25)	14	6 (60)	19	10 (38.5)
TEAEs suspected to be related to study drug	4	3 (18.8)	18	6 (60)	22	9 (34.6)
Serious TEAEs suspected to be related to the study drug	0	-	4	2 (20)	4	2 (7.7)
TEAEs leading to study drug discontinuation	0	-	2	2 (20)	2	2 (7.7)

*TEAE, events with a start date in the on-treatment period, or events present prior to but increased in severity in the on-treatment period; N, number of participants who received at least one dose of study treatment.

- Median duration of exposure of patients to iptacopan: Cohort A: 26.9 months, Cohort B: 29.4 months
- The majority of TEAEs were mild to moderate in severity
- One participant in Cohort B experienced serious pneumococcal pneumonia suspected to be related to iptacopan
- No cases of meningitis and/or meningococcal sepsis were reported in either cohort
- †One serious TEAE had a fatal outcome in Cohort A that led to early study discontinuation and was determined to be unrelated to iptacopan treatment

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Disclosures

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Abbreviations

AP, alternative pathway; b.i.d., twice-daily; C3G, C3 glomerulopathy; CI, confidence interval; CNI, calcineurin inhibitor; CS, corticosteroid; D, day; eGFR, estimated glomerular filtration rate; FMV, first morning void; h, hour; IA, interim analysis; M, month; MPA, mycophenolic acid; TEAE, treatment-emergent adverse event; UPCR, urine protein–creatinine ratio.