Efficacy and safety of iptacopan in patients with C3 glomerulopathy: 12-month results from the Phase 3 APPEAR-C3G study

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WCN25-AB-2041

KEY FINDINGS & CONCLUSIONS

- The study **met its primary endpoint**, demonstrating a statistically significant reduction in 24h UPCR with iptacopan treatment at 6 months vs. placebo, **sustained up to 12 months**
- Iptacopan showed a **sustained improvement in patients meeting the composite renal endpoint** (≥50% reduction UPCR + ≤15% reduction in eGFR at 12 months)
- **eGFR stabilized following iptacopan treatment** including participants randomized to placebo arm and then switched to iptacopan from Day 180 in the open-label period
- **Improvements in eGFR slopes were observed post-iptacopan treatment up to 12 months** compared to the pre-iptacopan treatment eGFR slope
- Iptacopan **showed nominal significance on glomerular C3 deposition reduction**
- Iptacopan was **well tolerated with a favorable safety profile** over 12 months which was consistent with previously reported data

This study is sponsored by Novartis Pharma AG
Poster presented at the ISN World Congress of Nephrology 2025 | 6–9 February 2025 | New Delhi, India.
Previously presented at American Society of Nephrology (ASN) Kidney Week 2024 | 23-27 October 24 San Diego, CA, USA

INTRODUCTION

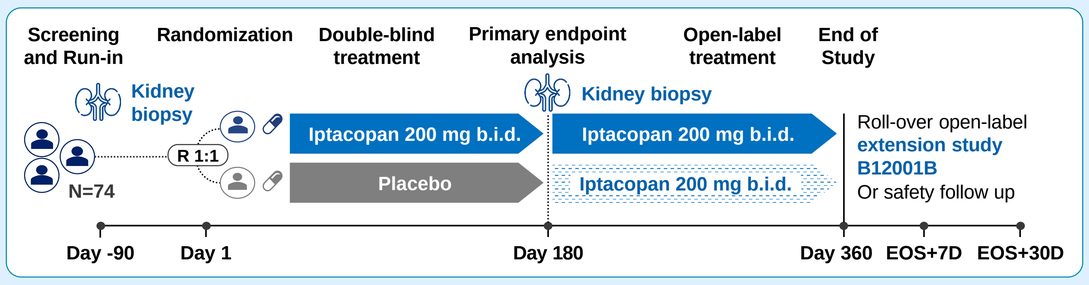
- C3G is an ultra-rare, chronic, and severe form of primary glomerulonephritis with a global annual incidence of 1–2 per million. C3G prevalence in US based on registry data is ~2–3 cases per million[1,2]
- Overactivation of the alternative pathway (AP) of the complement system leads to C3 deposition in the glomerulus triggering glomerular inflammation and injury[2–6]
- Currently, there are no treatment options approved for C3G[5]
  - KDIGO Glomerular Diseases guidelines recommend supportive care and immunosuppression, and participation in clinical trials is recommended for high-risk patients unresponsive to current treatment approaches[7]
- Iptacopan (LNP023; 200 mg twice daily [b.i.d.]) is an oral, proximal complement inhibitor that targets Factor B and inhibits the AP[8,9]

METHODS

Study design

- APPEAR-C3G (NCT04817618) was a randomized, double-blind, parallel-group, multicenter, placebo-controlled Phase 3 study to evaluate the efficacy and safety of iptacopan 200 mg b.i.d. vs placebo, on top of supportive care, in adult patients with C3G[10,11]
- **Here, we present the results from the final analysis at 12 months when all adult participants completed the open-label period of the study (Figure 1)**

Figure 1. Study design



Open-label period	Primary objective	• To evaluate the effect of iptacopan on proteinuria at 12 months
	Key secondary objectives	• To evaluate the effect at 12 months of iptacopan on a composite renal endpoint • To evaluate the safety and tolerability of iptacopan over 12-month treatment period

RESULTS

- High baseline estimated glomerular filtration rate (eGFR) across both treatment groups with higher urine protein-to-creatinine ratio (UPCR) in iptacopan arm **(Table 1)**

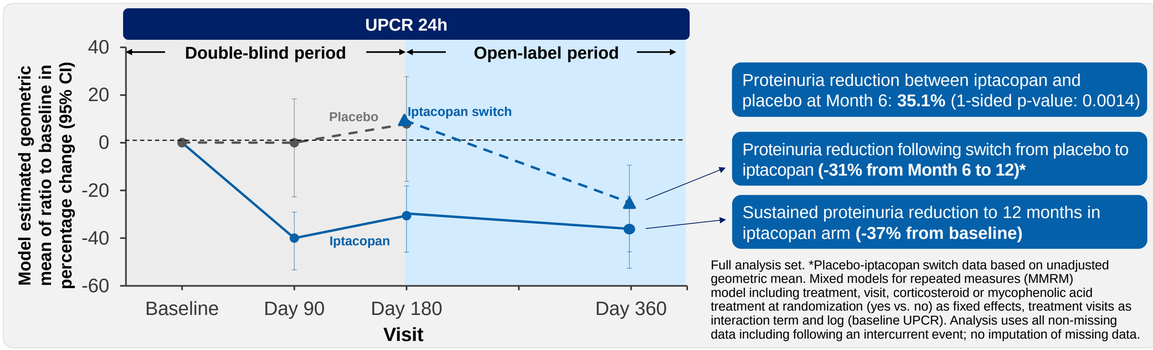
Table 1. Disease characteristics

		Iptacopan (N=38)	Placebo (N=36)
Baseline UPCR 24h (g/g) – Geo-mean (95%CI)		**3.33** (2.79, 3.97)	**2.58** (2.18, 3.05)
Baseline total urinary protein (24h) – n **(%)**	**≥3 g/day**	27 (71.1%)	21 (58.3%)
Baseline UPCR (24h) – n **(%)**	**≥3 g/g**	21 (55.3%)	11 (30.6%)
Baseline eGFR (mL/min/1.73m²) – Mean (SD**)**		**89.3** (35.20)	**99.2** (26.88)
Baseline eGFR – n **(%)**	**<90 mL/min/1.73m²**	19 (50.0%)	12 (33.3%)
Baseline eGFR – n **(%)**	**<60 mL/min/1.73m²**	10 (26.3%)	4 (11.1%)
Hypertension – n **(%)**		23 (60.5%)	18 (50.0%)
Age at C3G diagnosis – n **(%)**	**<18 years**	15 (39.5%)	6 (16.7%)
Time since first C3G diagnosis – n **(%)**	**<2 years**	15 (39.5%)	15 (41.7%)
Baseline RASi use – n **(%)**		37 (97.4%)	36 (100%)
Corticosteroid and/or mycophenolic acid at randomization	**Yes**	16 (42.1%)	17 (47.2%)
C3G subtype at diagnosis – n **(%)**	**C3GN**	26 (68.4%)	32 (88.9%)
	DDD	9 (23.7%)	1 (2.8%)
	Mixed C3GN/DDD	2 (5.3%)	2 (5.6%)

Primary endpoint

Statistically significant 24h UPCR reduction demonstrated at 6 months vs. placebo was sustained up to 12 months **(Figure 2)**

Figure 2. Proteinuria reduction up to 12 months

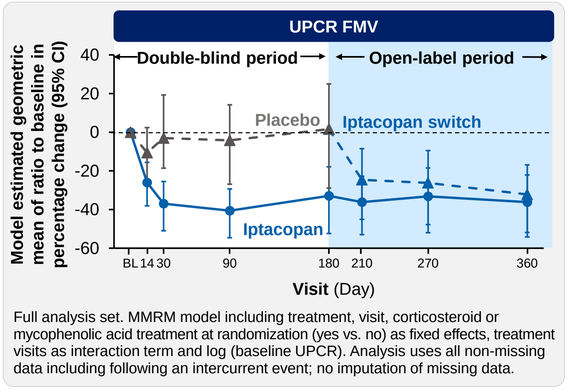


Full analysis set. *Placebo-iptacopan switch data based on unadjusted geometric mean. Mixed models for repeated measures (MMRM) model including treatment, visit, corticosteroid or mycophenolic acid treatment at randomization (yes vs. no) as fixed effects, treatment visits as interaction term and log (baseline UPCR). Analysis uses all non-missing data including following an intercurrent event; no imputation of missing data.

Supplementary analysis

Proteinuria reduction (UPCR FMV) observed at first visit after iptacopan initiation (**Figure 3**)

Figure 3. Proteinuria reduction (UPCR FMV) up to 12 months

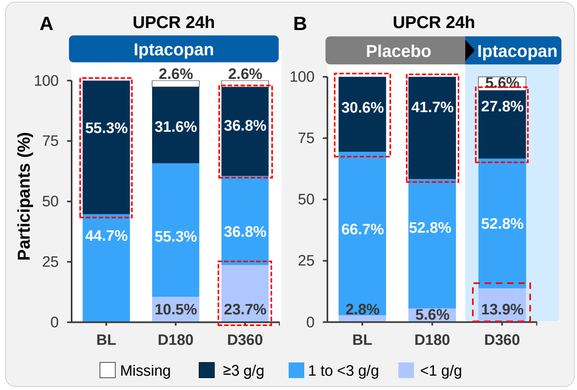


Full analysis set. MMRM model including treatment, visit, corticosteroid or mycophenolic acid treatment at randomization (yes vs. no) as fixed effects, treatment visits as interaction term and log (baseline UPCR). Analysis uses all non-missing data including following an intercurrent event; no imputation of missing data.

Post-hoc analysis

Improvement in all UPCR categories upon initiation of iptacopan (**Figure 4**)

Figure 4. Categorical change in UPCR 24h at Month 12

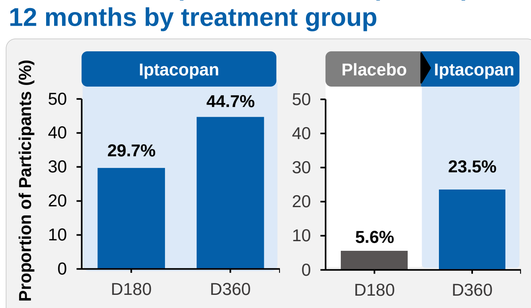


- **Decrease** in participants with nephrotic range proteinuria **(UPCR ≥3 g/g)** at Month 12 (-18%). **Increase** in participants achieving **UPCR <1 g/g** after 12 months (+24%) **(Figure 4A)**
- **Increase** in participants with nephrotic range proteinuria **(UPCR ≥3 g/g)** with placebo during double-blind (+11%) with subsequent **reduction** following switch to iptacopan in the open-label period (-14%). **Increase** in participants achieving **UPCR <1 g/g** after switching to iptacopan in the open-label period (+14%) **(Figure 4B)**
- At Day 360, the percentage of participants with nephrotic range proteinuria decreased and more participants achieved a <1 g/g level of proteinuria

Secondary endpoints

- Iptacopan showed a further improvement in participants meeting the composite renal endpoint≥ 50% UPCR reduction and stable eGFR (≤15% reduction) at 12 months **(Figure 5)**
- Iptacopan stabilized eGFR in placebo arm after switching to open-label iptacopan (**Figure 6**)

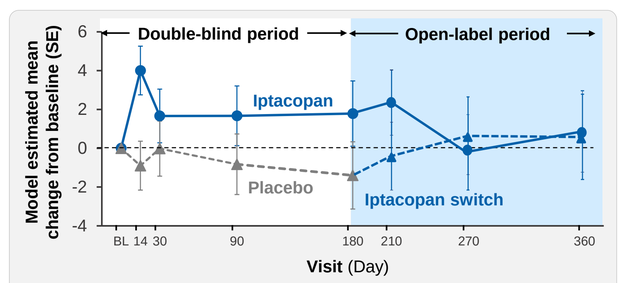
Figure 5. Proportion of participants who achieved composite renal endpoint up to 12 months by treatment group



Results driven by the ≥50% proteinuria reduction component

Full analysis set. *Composite endpoint defined as ≥50% UPCR reduction and stable eGFR (≤15% reduction). eGFR, estimated glomerular filtration rate; n, number of participants who reached the endpoint at designated visit.

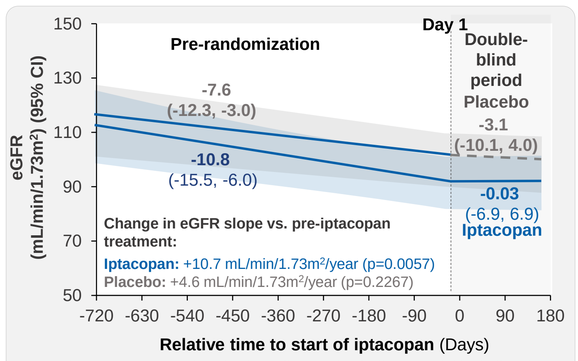
Figure 6. eGFR Change from Baseline to Month 12 (adjusted for baseline UPCR imbalance)



Post-hoc analysis. Full analysis set. MMRM model including treatment, visit, corticosteroid or mycophenolic acid treatment at randomization (yes v no) as fixed effects, treatment visits as interaction term and baseline eGFR and log (baseline UPCR) as covariates. Analysis uses all non-missing data including following an intercurrent event; no imputation of missing data.

Figure 7. eGFR slope by treatment group pre- and post-iptacopan treatment initiation up to 6 months

- Annualized eGFR slope change indicates an improvement in the iptacopan arm post-treatment initiation up to 6 months vs. historic slope decline



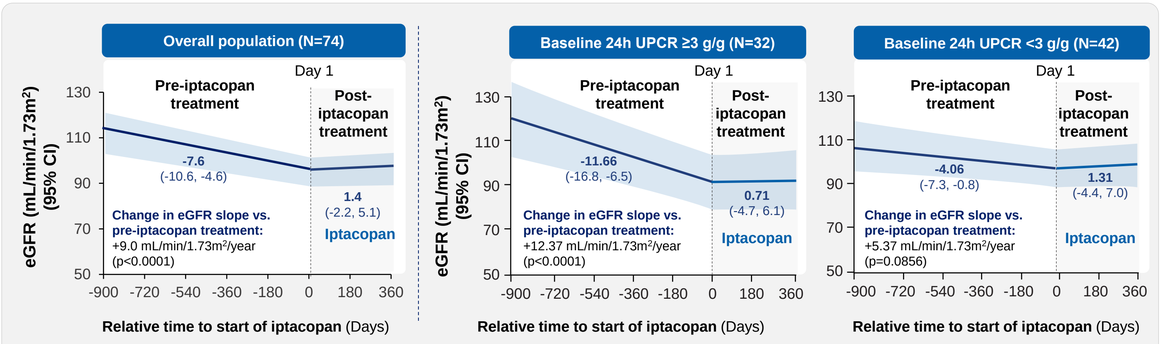
eGFR slopes per year analyzed using a linear mixed effects model including time (analysis day before or after change point (day 1 of iptacopan treatment) as a continuous covariate, participant-level intercept and slope (time) as random effects. Intercurrent events handled with a treatment policy strategy.

Table 3. Safety profile

	Iptacopan 200 mg b.i.d. 12 months N=38; n (%)	Iptacopan 200 mg b.i.d. Overall* N=74; n (%)
Number of participants with at least one TEAE	**32 (84.2)**	**56 (75.7)**
Suspected to be related to study medication	8 (21.1)	10 (13.5)
Severe AEs	**2 (5.3)**	**2 (2.7)**
SAEs	**4 (10.5)**	**6 (8.1)**
Blood culture positive (*Streptococcus pneumoniae*)	1 (2.6)	1 (1.4)
Infected bite	1 (2.6)	1 (1.4)
Chest discomfort	1 (2.6)	1 (1.4)
Retroperitoneal hematoma	1 (2.6)	1 (1.4)
Pneumococcal pneumonia/sepsis/septic shock	1 (2.6)	1 (1.4)
Acute left ventricular failure	1 (2.6)	1 (1.4)
Pneumonia	0	1 (1.4)
Drug abuse (amphetamine)	0	1 (1.4)
AEs leading to study drug discontinuation	**0**	**0**
Deaths	**0**	**0**

Numbers (n) represent counts of participants. *Includes TEAEs reported for participants randomized to iptacopan arm over the 12 months and participants that switched from placebo to iptacopan during the open-label period.

Figure 8. Overall population and across UPCR categories



eGFR slopes per year analyzed using a linear mixed effects model including time (analysis day before or after change point (Day 1 of iptacopan treatment) as a continuous covariate, participant-level intercept and slope (time) as random effects. Intercurrent events handled with a treatment policy strategy.

Table 2. C3 deposit score at 6 months vs. placebo (nominally significant)

					Iptacopan vs. Placebo	
	Treatment	N	n	Adjusted mean (95% CI)	Adjusted mean difference (95% CI)	1-sided p-value
Glomerular C3 deposition score	Iptacopan	35	32	**-0.781** (-1.811, 0.250)	**-1.875** (-3.298, -0.452)	**0.0053**
	Placebo	36	35	**1.094** (0.111, 2.078)		

Change from baseline in C3 deposit score was analyzed using an analysis of covariance (ANCOVA) model which included treatment, corticosteroid or mycophenolic acid treatment at randomization (yes vs. no) as fixed effects and baseline C3 deposit score as covariate.

Acknowledgements

- Authors thank the **patients, their families, investigators and staff** at participating study sites
- Professional medical writing assistance was provided by **Aditya Pramod (Novartis, India)** and **Andrew Jobson (Novartis Pharmaceuticals UK Limited),** and funded by Novartis Pharma AG, Basel, Switzerland.

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Disclosures

Carla M Nester: clinical trial research support from Biocryst, Achillion, Novartis, Apellis, consulting fee from Silence Therapeutics; and participated on data safety monitoring board of Kira.

Richard J H Smith: research funding from NIH, consultant for Novartis.

David Kavanagh: scientific founder of and hold stocks in Gyroscope Therapeutics. He has received consultancy income from Gyroscope Therapeutics, Alexion Pharmaceuticals, Novartis, Apellis and Sarepta. His spouse works for GSK.

Marina Vivarelli: honoraria for advisory boards and consulting fees, participation in clinical studies sponsored by the following pharmaceutical companies: Achillion, Alexion Pharmaceuticals, Apellis, Bayer, Catalyst, ChemoCentryx, PureSpring, Novartis, Roche, Retrophin/Travere, GSK, Vifor, BioCryst Pharmaceuticals, Chinook Therapeutics.

Giuseppe Remuzzi: consulting fees from Alexion Pharmaceuticals, BioCryst Pharmaceuticals, and Silence Therapeutics.

Ming-Hui Zhao: honoraria for consulting boards and consulting fees: AstraZeneca, Novartis; Roche; BeiGene, SanReno, Kira.

Edwin KS Wong: received fees for consultancy or speakers' agreements from Alexion Pharmaceuticals / Apellis / Arrowhead / BioCryst / Novartis.

Andrew S Bomback: consulting honoraria from Achillion, Alexion, ChemoCentryx Therapeutics, Novartis, Silence, Catalyst, and Principio.

Yaqin Wang, Induja Krishnan: employees and stockholders of Novartis.

Matthias Meier, Nicholas J.A. Webb, Angelo J. Trapani: employees of Novartis at the time of abstract submission.

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.

Abbreviations

AE, adverse event; AP, alternative pathway; b.i.d., twice daily; BL, baseline; C3, complement component 3; C3G, C3 glomerulopathy; C3GN, complement component 3 glomerulonephritis; CI, confidence interval; DDD, dense deposit disease; D, day; eGFR, estimated glomerular filtration rate; EOS, end of study; FMV, first morning void; MMRM, mixed model for repeated measures; N, number of all participants included in the analysis; n, participants; RASi, renin–angiotensin system inhibitor; SD, standard deviation; SAE, serious adverse event; SE, standard error; TEAE, treatment-emergent adverse event; UPCR, urine protein–creatinine ratio; US, United States.