12M interim analysis of an open-label, non-randomized extension of a Ph 2 study to evaluate the long-term efficacy, safety and tolerability of iptacopan in subjects with C3G

TH-PO505

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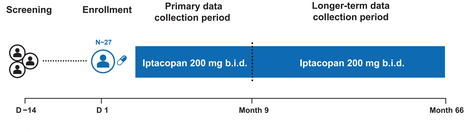
Introduction

- Complement 3 Glomerulopathy (**C3G**) is a complex, chronic, rare primary glomerulonephritis, secondary to **dysregulation of the alternative complement pathway (AP)**, with an estimated worldwide annual incidence of 1–2 cases per million[1, 2]
- Iptacopan (LNP023) is an oral, first-in-class, highly potent proximal complement inhibitor that specifically binds factor B and inhibits the AP[3]
- We have previously reported data from a Phase 2 proof of concept (PoC) study in patients with native and recurrent C3G (NCT03832114) demonstrating iptacopan's potential as an effective treatment option that targets the pathogenesis of the disease in these patient populations. A 12-week course of iptacopan resulted in:
  - **A 45% reduction in proteinuria** (p=0.0003), inhibition of AP activity and stabilization of eGFR in patients with native C3G[4,5]
  - **Reduction in C3 deposit scores** on kidney biopsy in patients with recurrent C3G after kidney transplantation (p=0.03)[4]
- Patients who completed the 12-week Phase 2 study were given the opportunity to continue treatment and were rolled over into this extension study (NCT03955445). Here we present the effects of 12 months of iptacopan treatment (3 months in the Phase 2 study plus 9 months treatment in the extension study).

Study design

- This Phase 2 open-label, non-randomized study was a multicenter **extension study**. Adults with native (Cohort A) or recurrent C3G post kidney transplant (Cohort B) received iptacopan for ≥12 weeks before entering this extension study



b.i.d., twice daily; D, day.

Primary objective

Efficacy: To assess the effect of iptacopan on a composite endpoint* of:
1) stable/improved eGFR (≤10% reduction from baseline),
2) ≥50% reduction from baseline in UPCR, and
3) ≥50% increase from baseline in serum C3 after 12 months of treatment

Safety: To evaluate the long-term safety and tolerability of iptacopan in patients with C3G

Key secondary objectives

To assess the long term-effects of iptacopan on:
- Kidney function (log-transformed UPCR, UACR and eGFR)
- Changes in biomarkers of the complement pathway (C3, Bb, Wieslab, sC5b-9), measured in plasma or serum
- Urine markers of kidney damage (lipocalin-2 [NGAL]/creatinine)

Population

Patients in Cohort A had proteinuria ≥100 mg/mmol despite treatment with ACEi or ARB, reduced C3 at screening (<77 mg/dL) and all patients had biopsy-confirmed C3G and eGFR ≥30 mL/ min/1.73 m²

*Initiation of treatment with eculizumab or any other complement pathway modifying agent designates the participant as not meeting the composite renal endpoint.

Baseline characteristics

		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 (%)	White	16 (100)	9 (90.0)
	American Indian or Alaska Native		1 (10.0)
eGFR (ml/min/1.73 m²)*	Mean (SD)	70.1 (35.10)	54.0 (17.17)
	Median (Range)	64.8 (28–134)	59.6 (27–74)
24h UPCR (g/mol)†	Mean (SD)	454.0 (242.16)	121.0 (188.29)
	Median (Range)	390.6 (199–1019)	18.4 (9–445)
FMV UPCR (g/mol)†	Mean (SD)	408.3 (304.35)	98.0 (182.55)
	Median (Range)	323.6 (82–988)	9.0 (5–493)
Serum C3 (g/L)‡	Mean (SD)	0.3 (0.22)	0.6 (0.26)
	Median (Range)	0.24 (0.02–0.69)	0.55 (0.17–1.00)

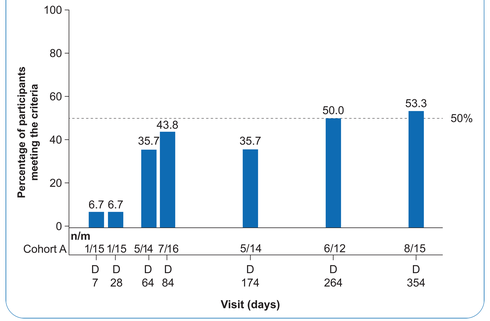
*Normal eGFR: ≥90 mL/min/1.73 m²; †Normal UPCR: <22.6 g/mol (g/g = g/mol × 0.00885); ‡Normal serum C3: 0.9–1.8 g/L.
eGFR, estimated glomerular filtration rate; FMV, first morning void; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

- Of 27 patients completing the 12-week Phase 2 study, 26 (n=16 Cohort A, n=10 Cohort B) entered the extension for treatment with iptacopan 200 mg b.i.d.
- At baseline, median UPCR was within the normal range for Cohort B but not Cohort A

53% of native C3G patients met the composite renal endpoint

Following 12 months of treatment with iptacopan 200 mg b.i.d., 8 of 15 (53%) native C3G patients (Cohort A) met all three composite renal endpoint criteria for UPCR, eGFR, and C3

- At 12 months, 53.3% (8/15) of Cohort A patients had met the individual component for UPCR and 93.8% (15/16) for eGFR
- By Day 21, 100% (16/16) of patients had met the individual component of C3



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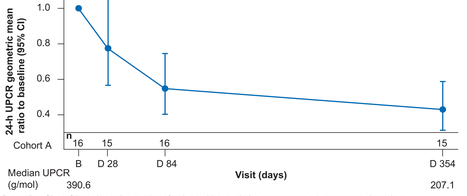
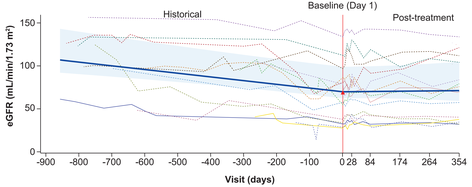
Long-term treatment with iptacopan results in sustained improvements in composite renal endpoints in native C3G

Proteinuria was reduced by 57% (p<0.0001) following 12 months of iptacopan treatment in Cohort A



B, baseline; CI, confidence interval; n, number of patients with non-missing measurements at assessment timepoints; UPCR, urine protein-to-creatinine ratio. UPCR is from 24-hour urine collection. Analyzed using a mixed model for repeated measures.

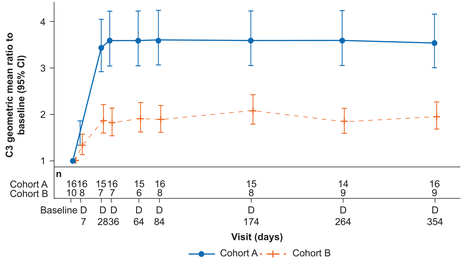
eGFR decline was reversed with an improvement of 1.3mL/min/1.73 m²/year from baseline in Cohort A (p=0.0233 for the change in the eGFR slope pre-and post treatment)



n=14. Study visits were Days 174, 264, 354, 444 (3, 6, 9, 12 months in extension). Participants with only historical data were included. Blue shaded area is 95% Confidence Band and thick blue line is Predicted Fit. Analyzed using a general linear model.

- The rate of decline in eGFR during 2 years prior to iptacopan initiation was -15.73mL/min/1.73m²/year (p=0.0014), consistent with the known natural history of native C3G.

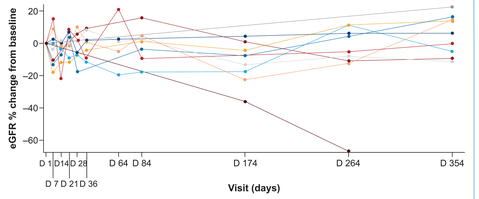
C3 levels increased by more than 250% in Cohort A at 12 months (C3 was normalized in 8/16 pts in Cohort A and 7/9 pts in Cohort B)



CI, confidence interval; n, number of patients with non-missing measurements at assessment timepoints. Analyzed using a mixed model for repeated measures.

- The mean (SD) values of C3 biomarker increased from 0.31 (0.22) g/L at baseline to 0.85 (0.36) g/L at 12 months in Cohort A, and from 0.62 (0.29) g/L to 1.12 (0.21) g/L in Cohort B

eGFR was stable in recurrent C3G at 12 months



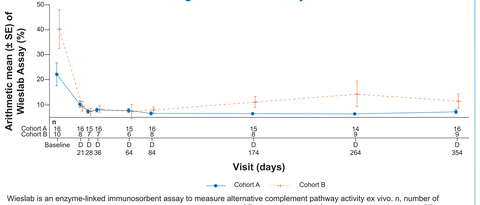
n=10. eGFR, estimated glomerular filtration rate.

- In Cohort B, eGFR was stable and C3 levels increased by 96%
- eGFR was stable for 12 months in 9 of 10 patients; 1 patient progressed to kidney failure
  - Proteinuria reduction was not assessed in Cohort B as median baseline proteinuria was normal (18.4 g/mol)

Biomarkers of AP activity and kidney damage

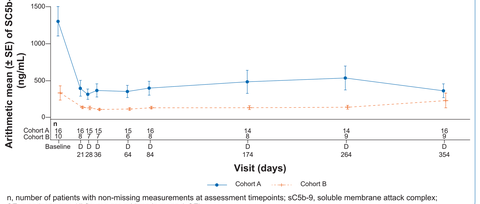
- Selective inhibition with iptacopan substantially inhibited the AP as demonstrated by Wieslab activity (p<0.0001 at 1 year treatment in both cohorts), Bb (p=0.9827 and p=0.0032 in Cohort A and B, respectively) and plasma sC5b-9 (p<0.0001 and p=0.0023 in Cohort A and B, respectively) levels
- Levels of lipocalin-2 (NGAL)/Creatinine, a biomarker of kidney damage, were lowered (data not shown), suggesting iptacopan can protect against kidney damage

Figure A: Wieslab Assay



Wieslab is an enzyme-linked immunosorbent assay to measure alternative complement pathway activity ex vivo. n, number of patients with non-missing measurements at assessment timepoints; SE, standard error. All figures are arithmetic mean (±SE).

Figure B: sC5b-9



n, number of patients with non-missing measurements at assessment timepoints; sC5b-9, soluble membrane attack complex; SE, standard error. All figures are arithmetic mean (±SE).

Iptacopan was generally well-tolerated

	Cohort A N=16		Cohort B N=10		Overall N=26	
	Number of events	n (%)	Number of events	n (%)	Number of events	n (%)
Participants with at least one TEAE	81	15 (93.8)	59	9 (90.0)	140	24 (92.3)
Mild	74	15 (93.8)	42	9 (90.0)	116	24 (92.3)
Moderate	6	5 (31.3)	12	5 (50.0)	18	10 (38.5)
Severe	1	1 (6.3)	5	3 (30.0)	6	4 (15.4)
Serious TEAEs	3	2 (12.5)	6	3 (30.0)	9	5 (19.2)
TEAEs reported as related to study drug	5	3 (18.8)	15	5 (50.0)	20	8 (30.8)
Serious TEAEs reported as related to study drug	0	0	3	1 (10.0)	3	1 (3.8)

*Note: Includes patients in the safety analysis set as of Jan 26, 2022, including any AEs reported in the core Phase 2 study.
n, number of patients with at least 1 TEAE; TEAE, treatment-emergent adverse event.

- Most treatment-emergent adverse events (TEAEs) were of mild severity in both cohorts; however, a greater proportion of AEs were moderate or severe in Cohort B mostly due to the mandatory immunosuppressive background therapy (5 and 15 treatment-emergent AEs were study drug-related in Cohorts A and B, respectively)
- In Cohort A, 1 death was reported during the treatment period as a result of cardiac arrhythmia, and was determined to be unrelated to iptacopan treatment
  - Concomitant medications with a risk for arrhythmia were methylphenidate and velafaxine
- In Cohort B, 3 patients had TEAEs that led to study drug interruption, and 1 patient had a serious TEAE (acute kidney injury) that led to study drug discontinuation
- One patient from Cohort B had 3 serious TEAEs which were suspected to be related to iptacopan; pneumonia, acute respiratory distress syndrome and sepsis caused by encapsulated bacteria *S. pneumoniae*

Conclusions

- In patients with C3G and native kidneys, long-term treatment (12 months) with iptacopan resulted in further proteinuria reduction (57% [p<0.0001]) and eGFR improvement (by +6.83 mL/min/1.73 m² [p=0.0174]) beyond that previously reported following 12 weeks of treatment
  - Treatment with iptacopan reversed the rapid rate of eGFR decline in these patients
- These improvements in kidney function were associated with **substantial inhibition** of the **alternative complement pathway and normalization of serum C3 levels** in many patients
- In patients with recurrent post-transplant C3G, eGFR remained stable with long-term iptacopan treatment along with sustained AP inhibition
- Iptacopan was generally **well-tolerated** with most AEs being of mild or moderate severity
  - Overall, 5 patients experienced 9 serious TEAEs and there was 1 death unrelated to iptacopan treatment
- These results support further evaluation of iptacopan in the ongoing **Phase 3 APPEAR-C3G** trial[6] (NCT04817618), which is **currently recruiting patients**, and confirm the efficacy and safety for long-term treatment of C3G with iptacopan

Disclosures

CMN, ChemoCentryx , Alexion Pharmaceuticals, Novartis, Retrophin, Appellis, BioCryst, Kira; **UE**, Astellas, Biotest, Chiesi and Novartis; **AK**, Novartis, GSK, Astra-Zeneca, Bohringer-Ingelheim , Pfizer; **MQD**, nothing to declare; **LL**, Alexion Pharmaceuticals, AstraZeneca, Biogen, BMS, GSK, Kezar, Novartis, Pfizer; **MP**, Novartis, Travere, Alexion, Silence, Glaxo-Smith Kline, Vifor, Otsuka; **GR**, Akebia Pharmaceuticals, Alexion Pharmaceuticals, AstraZeneca, BioCryst Pharmaceuticals, Boehringer Ingelheim, Janssen Research & Development LLC, Menarini Ricerche Spa, Otsuka, Silence Therapeutics, Novartis; **MJS**, Boehringer, AstraZeneca, Novo-Nordisk, Esteve, Vifor, Bayer, Mundipharma, Fresenius Medical Care Renal Pharma, Boehringer, Ingelheim Lilly, Jansen, ICU Medical, Travere Therapeutics, CKJ; **EKW**, Alexion, Apellis, Biocryst and Novartis. **JL**, **MM**, **RT**, **GJ**, **AB**, **AJT** and **NJW** are employees and stockholders of Novartis. This analysis was funded by Novartis Pharma AG.

Acknowledgments

Professional medical writing and editorial assistance was provided by Lorna Mulvey, PhD, at Novartis Ireland Limited, Dublin, Ireland and Nagabhushana Aranthamurthy, PhD, Novartis Healthcare Pvt. Ltd., Hyderabad, India, funded by Novartis Pharma AG, Basel, Switzerland

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; AP, alternative pathway; ARB, angiotensin receptor blockers; b.i.d., twice daily; C3, complement 3; C3G, C3 glomerulopathy; CI, confidence interval; D, day; eGFR, estimated glomerular filtration rate; FMV, first morning void; NGAL, neutrophil elatinase-associated lipocalin; sC5b-9, soluble membrane attack complex; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; UACR, urine albumin-creatinine ratio; UPCR, urine protein-to-creatinine ratio

Presented at the American Society of Nephrology Kidney Week 2022, Orlando, FL, November 3–6, 2022

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