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An open-label, non-randomized extension study to evaluate the long-term efficacy, safety, and tolerability of LNP023 in subjects with C3 glomerulopathy: Interim analysis of a Phase 2 study

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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 study in patients with native and recurrent C3G (NCT03832114) demonstrating the potential of iptacopan 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). Herein 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)

Methods

- 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

Primary objectives

- **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
  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:
  1. Kidney function (log-transformed UPCR, UACR, and eGFR)
  2. Changes in biomarkers of the complement pathway (C3, Bb, Wieslab, sC5b-9), measured in plasma or serum
  3. 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 (<81 mg/dL), and all patients had biopsy-confirmed C3G and eGFR ≥30 mL/min/1.73 m^2

Results

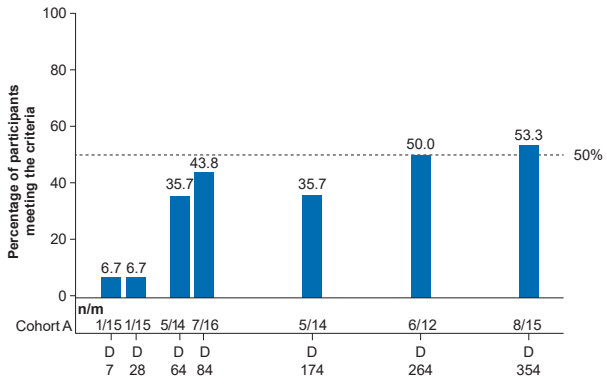
Baseline characteristics

- 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 bid
- At baseline, median UPCR was within the normal range for Cohort B but not Cohort A

Conclusions

- In patients with native C3G, 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 m^2 [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

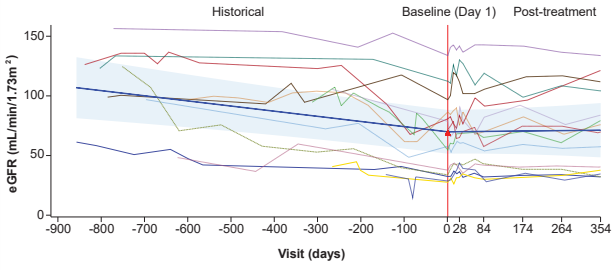
Figure 1. Following 12 months of treatment with iptacopan 200 mg bid, 8 of 15 (53%) native C3G patients (Cohort A) met all 3 composite renal endpoint criteria for UPCR, eGFR, and C3



m=number of participants at each time point. n=number of participants meeting the criteria at each time point

- At 12 months, 53.3% (8 of 15) of Cohort A patients had met the individual component for UPCR and 93.8% (15 of 16) for eGFR (**Figure 1**)
- By Day 21, 100% (16 of 16) of patients had met the individual component of C3

Figure 2. The eGFR slope based on historical data changed after iptacopan initiation and eGFR decline was reversed (p=0.0233)



Participants (Cohort A) with only historical data were included. Blue shaded area is 95% Confidence Band and thick blue line is Predicted Fit

Results

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
- The eGFR slope changed (**Figure 2**)
- C3 levels increased by more than 250% in Cohort A at 12 months (C3 was normalized in 8 of 16 patients in Cohort A & 7 of 9 patients in Cohort B)
  - 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

- 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) and plasma sC5b-9 (p<0.0001 and p=0.0023 in Cohorts A and B, respectively) levels
- Reductions of Bb biomarker levels were observed in both cohorts, though statistically significant reduction was only seen in Cohort B (p=0.9827 and p=0.0032 in Cohort A and B, respectively)
- Cohort A participants had elevated levels of urinary lipocalin-2/NGAL compared to Cohort B and were reduced by up to approximately 60% upon treatment with iptacopan suggesting reduced kidney injury

Iptacopan was generally well tolerated

Table 1. Treatment-emergent adverse events†

TEAEs	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 1 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)

- Most 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 TEAEs were study drug-related in Cohorts A and B, respectively; **Table 1**)
- 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 venlafaxine
- 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*

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

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; AP, alternative pathway; ARB, angiotensin receptor blockers; bid, twice daily; C3, complement 3; C3G, C3 glomerulopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; FMV, first morning void; NGAL, neutrophil gelatinase-associated lipocalin; sC59-b, soluble membrane attack complex; SD, standard deviation; SE, standard error; TEAE, treatment-emergent AE; UACR, urine albumin-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

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Disclosures

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