Zanubrutinib for the Treatment of Primary Membranous Nephropathy: Results of a Single-Arm Feasibility Study

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BACKGROUND

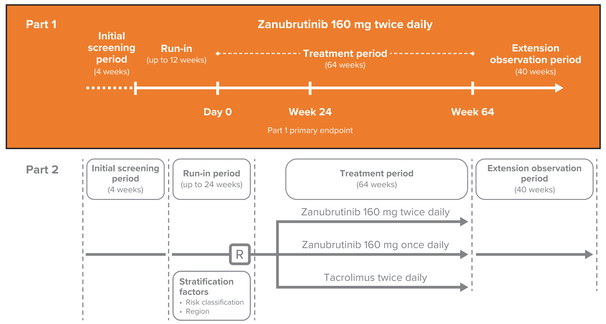
- Primary membranous nephropathy (PMN) is an autoimmune glomerular disease; it is characterized by proteinuria, hypoalbuminemia, glomerular injury, and, in most patients, elevated serum anti-phospholipase A2 receptor (anti-PLA2R) antibodies[1]
- Approximately 80% of patients with PMN present with nephrotic syndrome.[1] Left untreated, membranous nephropathy results in end-stage kidney disease in approximately 35% of patients within 10 years,[1] increasing the risk of life-threatening thromboembolic and cardiovascular events
- Despite this, there are limited treatment options and no formally approved pharmacological therapies for PMN
- B-cell dysfunction plays a key role in the development of PMN, and treatments targeting B cells have been shown to induce clinical remission[2]
- Bruton tyrosine kinase (BTK) plays a key role in B-cell modulation[3,4] and has emerged as a potential therapeutic target in PMN and other autoimmune diseases
- The efficacy and safety of zanubrutinib, a highly selective and irreversible inhibitor of BTK,[3,4] is currently being evaluated in a two-part, phase 2/3 study in patients with PMN. Results from part 1 of the study are presented here

METHODS

Study design, population, and treatment

- Part 1 was an open-label, single-arm study investigating the preliminary efficacy and safety of zanubrutinib in the treatment of PMN (**Figure 1**)
  - Eligible patients for part 1 were adults (aged 18–75 years) with an anti-PLA2R antibody level of >50 RU/mL and a urinary protein-creatinine ratio (UPCR) of >3.5 mg/mg based on 24-hour urine collection
  - After a 12-week run-in period with optimal supportive care, patients received zanubrutinib 160 mg twice daily for up to 64 weeks; this was followed by a 40-week observation period
- Part 2 is an ongoing, randomized, open-label, active-controlled (tacrolimus) study investigating the efficacy and safety of zanubrutinib 160 mg twice daily or zanubrutinib 160 mg once daily in patients with PMN

Figure 1. Study design



R, randomization.

Endpoints

- The primary efficacy endpoint was change from baseline in UPCR at 24 weeks
- Secondary/additional efficacy endpoints included immunological response status at 24 weeks (i.e., an anti-PLA2R antibody titer <14 RU/mL), and clinical remission status at 24 weeks (complete remission was defined as an UPCR ≤0.3 mg/mg and stable estimated glomerular filtration rate [eGFR]; partial remission was defined as an UPCR of >0.3 to ≤3.5 mg/mg [with ≥50% decrease from baseline] and stable eGFR)
- Safety was assessed by monitoring the incidence and severity of adverse events (AEs)

RESULTS

Study population

- In total, 30 patients were enrolled in the study; 9 (30.0%) patients discontinued study treatment prematurely (4 [13.3%] due to treatment failure; 3 [10.0%] due to patient decision; and 2 [6.7%] due to adverse events). 25 (83.3%) completed the initial 24-week period. As of August 22, 2024, the median duration of treatment was 31.4 weeks (range 4.0–64.0)
- Baseline demographics and disease characteristics are presented in **Table 1**. Most patients were from Asia and had median UPCR of 7.5 mg/mg, median serum anti-PLA2R antibody titer of 161.0 RU/mL, median serum albumin of 22.9 g/L, and median eGFR of 85.2 mL/min/1.73 m^2

Table 1. Baseline demographics and disease characteristics

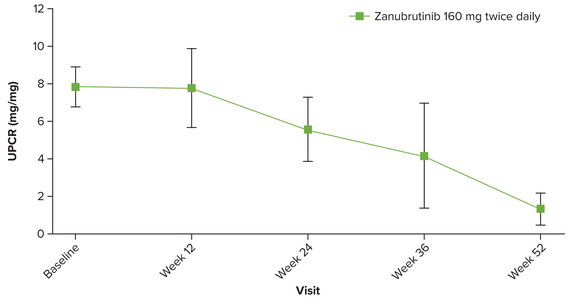
Characteristic	Zanubrutinib 160 mg twice daily (N=30)
Age, median (range), years	46.5 (32–74)
Age <50 years, n (%)	17 (56.7)
Age ≥50 years, n (%)	13 (43.3)
Male sex, n (%)	20 (66.7)
Race, n (%)	
Asian	28 (93.3)
White	2 (6.7)
Region, n (%)	
Asia	27 (90.0)
Europe	2 (6.7)
North America	1 (3.3)
UPCR, median (range), mg/mg	7.5 (3.6–14.8)
Serum anti-PLA2R antibody titer, median (range), RU/mL	161.0 (51.4–1219.8)
Serum albumin, median (range), g/L	22.9 (15.0–42.3)
eGFR, median (range), mL/min/1.73 m^2	85.2 (39.8–123.0)
Time from initial diagnosis to study entry, median (range), months	3.1 (0.4–95.7)
Prior PMN treatment, n (%)	
Glucocorticoids	2 (6.7)

eGFR, estimated glomerular filtration rate; **anti-PLA2R**, anti-phospholipase A2 receptor; **PMN**, primary membranous nephropathy; **UPCR**, urinary protein-creatinine ratio.

Efficacy

- Mean UPCR decreased by week 24 with further decreases up to 52 weeks (**Figure 2**). At 24 weeks, the mean UPCR change from baseline was –1.7 mg/mg (SD, 3.7), which represents a 23.8% reduction
- Over 24 weeks, seven (23.3%) patients achieved partial remission; no patients achieved complete remission

Figure 2. Mean UPCR by analysis visit

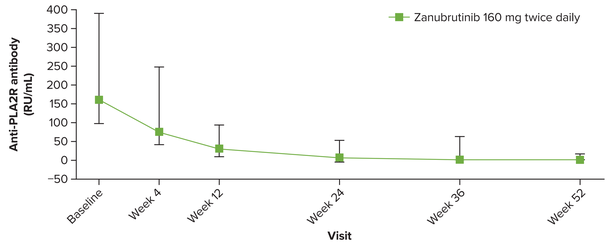


Patients	30	29	25	14	4

Error bars represent the 95% confidence interval. **UPCR**, urinary protein-creatinine ratio.

- The immunological response rate at 24 weeks was 46.7% (95% confidence interval 28.3–65.7; 14/30 patients), with 24/30 (80.0%) patients showing a ≥50% reduction from baseline in serum anti-PLA2R antibody levels and 18/30 (60.0%) showing a ≥90% reduction. Reduced serum anti-PLA2R antibody levels were maintained up to 52 weeks (**Figure 3**)

Figure 3. Median serum anti-PLA2R antibody titer by analysis visit

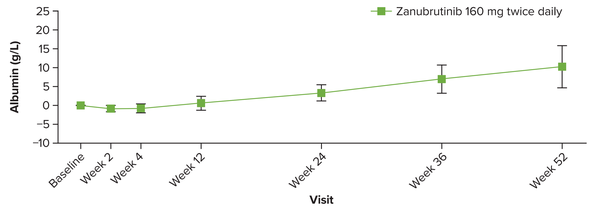


Patients	30	30	28	26	11	4

Error bars represent interquartile range. **anti-PLA2R**, anti-phospholipase A2 receptor.

- Mean serum albumin demonstrated a change from baseline of 3.5 g/L (standard deviation 5.6) at 24 weeks. As with the changes in serum anti-PLA2R antibody levels, increases were maintained up to 52 weeks (**Figure 4**)
- eGFR was stable throughout the 52-week period (**Figure 5**)

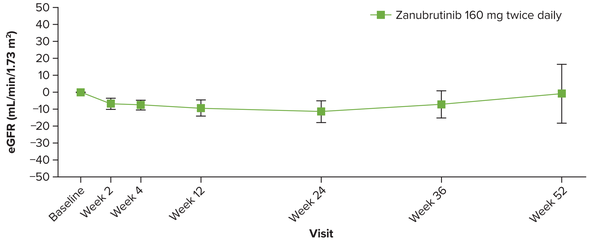
Figure 4. Mean change from baseline in serum albumin



Patients	30	29	29	29	26	14	4

Error bars represent the 95% confidence interval.

Figure 5. Mean change from baseline in eGFR



Patients	30	29	29	29	26	14	4

Error bars represent the 95% confidence interval. **eGFR**, estimated glomerular filtration rate.

CONCLUSIONS

- Findings from part 1 of this two-part, phase 2/3 study demonstrate that zanubrutinib is generally well tolerated with promising efficacy in patients with primary PMN
- These results support the continued evaluation of zanubrutinib in patients with PMN

Safety

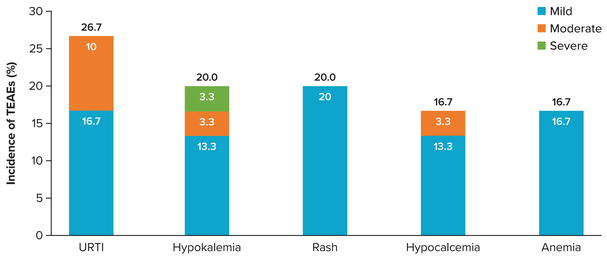
- Overall, 26 (86.7%) patients experienced a treatment-emergent AE (TEAE) (**Table 2**), the most common being upper respiratory tract infection (8 [26.7%]), hypokalemia (6 [20.0%]), and rash (6 [20.0%]) (**Figure 6**)
- Most AEs (73.3%) were mild to moderate in severity (**Figure 6**). Four patients had severe TEAEs (pneumonia, hypokalemia, and cerebral infarction in one patient, and one each of hypoproteinemia, generalized edema, and blood creatine phosphokinase increased in the other three patients). There were no fatal AEs

Table 2. Safety summary

AE category, n (%)	Zanubrutinib 160 mg twice daily (N=30)
Any TEAE	26 (86.7)
Leading to dose modification	7 (23.3)
Leading to discontinuation	2 (6.7)
Serious	5 (16.7)
Any TRAE	15 (50.0)
Severe	2 (6.7)
Serious	2 (6.7)

AE, adverse event; **TEAE**, treatment-emergent adverse event; **TRAE**, treatment-related adverse event.

Figure 6. Most commonly reported TEAEs (occurring in ≥15% of patients) and their severity



TEAE, treatment-emergent adverse event; **URTI**, upper respiratory tract infection.

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DISCLOSURES

RL reports employer: Stanford University; consultancy: Calliditas Inc, Chinook (Novartis) Inc, Omeros Inc, Otsuka Inc, Alexion Inc, Travere Inc, Vera Inc, Novartis, Aurinia, Visterra, Alpine Bio, and Beigene; Research funding: NIH, Roche, Otsuka, Calliditas, Travere, Alexion Chinook (Novartis), Vera, and Beigene.

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