Zetomipzomib Demonstrates Clinically Meaningful Improvement in UPCR in Nephrotic Range Proteinuria Patients: Results from the Open-label MISSION Study

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INTRODUCTION

- Zetomipzomib, a first-in-class, small molecule selective inhibitor of the immunoproteasome has demonstrated anti-inflammatory and immunomodulatory potential without evidence of immunosupression[1,2]
- In NZB/W murine models of SLE/LN, immunoproteasome inhibition resulted in complete resolution of proteinuria and down regulation of genes associated with tissue damage in the glomerulus and tubulointerstitium[1]
- Results previously reported on the Phase 2, open-label MISSION study (NCT03393013; KZR-616-002) evaluating the efficacy, safety and tolerability of zetomipzomib in active proliferative LN demonstrated meaningful renal responses[3]

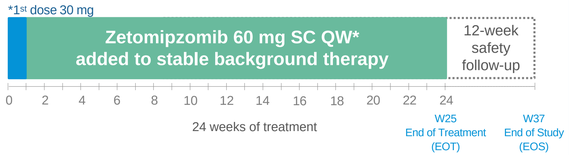
AIM

- Prospective cohorts have shown that patients with LN and nephrotic range proteinuria at baseline have a lower probability of achieving renal response[4]. These patients may require more time due to slower proteinuria recovery
- A post-hoc analysis of MISSION patients with nephrotic range proteinuria is presented here

METHOD

- MISSION Phase 2 study open-label evaluated zetomipzomib 60 mg administered subcutaneously (SC) once weekly (QW) for 24 weeks (1st dose: 30 mg) in adult patients with active proliferative LN (Class III or IV ± Class V) with baseline 24-hour urine protein to creatinine ratios (UPCR) ≥1.0 mg/mg despite stable background therapy (Figure 1)
- The primary endpoint was the number of patients with ≥50% reduction in UPCR from baseline after 24 weeks of treatment (Overall Renal Response [ORR])
- Safety, tolerability, 24-hour UPCR, renal response parameters, eGFR, SLE disease activity and biomarkers were measured
- Nephrotic range proteinuria was defined as UPCR ≥3.0 mg/mg at baseline as per KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

FIGURE 1: MISSION Phase 2 Open-label Study Design



Patients in MISSION Phase 2 did not receive standard LN induction therapy and steroid taper was not protocol-mandated

RESULTS

- 21 patients enrolled in protocol amendment 4 received ≥1 dose of zetomipzomib (safety population) and 4 patients discontinued before end of treatment (evaluable population, n=17)
- At baseline, 4 patients had nephrotic range proteinuria with 3 patients having hypoalbuminemia (mean serum albumin: 3.0 g/dL)
  - Patients had mean durations of LN (4.1 years) with mean 24-hour UPCR of 5.8 mg/mg, mean protein excretion of 5.6 g/day, mean blood pressure of 124/81 mmHg and mean eGFR of 122.5 mL/min/1.73 m^2
  - One patient had Class III, two patients with Class IV and one patient with Class III + V LN
  - Concomitant medications for all patients included corticosteroids (CS) (mean dose: 19.8 mg/d), mycophenolate mofetil or mycophenolic acid, hydroxychloroquine, and antihypertensives (ACE inhibitors [n=1]; ARBs [n=3])

TABLE 1: Post-hoc Analysis Demonstrated Meaningful Renal Responses in Patients with Nephrotic Range Proteinuria

Renal Response, n (%)	Patients with Nephrotic Range Proteinuria (n=4)	Overall MISSION Phase 2 Evaluable Population (n=17)
Overall Renal Response (ORR)^		
Week 25 (EOT)	3 (75)	11 (64.7)
Week 37 (EOS)	3 (75)	15 (88.2)
Complete Renal Response†		
Week 25 (EOT)	0	6 (35.3)
Week 37 (EOS)	0	7 (41.2)

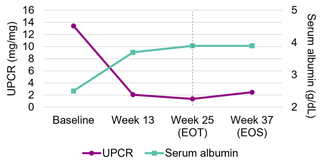
^ORR: ≥50% reduction in UPCR compared to baseline. †CRR: UPCR≤0.5, eGFR ≥60 mL/min/1.7m^2 or no worsening of eGFR from baseline of ≥25%, prednisone (or equivalent) ≤10 mg and no use of prohibited medication. *Evaluable population (n=17) are patients that did not withdraw before week 25 in amendment 4 of the open-label MISSION phase 2 study; patients received 24 weeks of zetomipzomib; end-of-treatment assessments performed at week 25.*

TABLE 2: Zetomipzomib Treatment Demonstrated Clinically Meaningful Responses in Patients with Nephrotic Range Proteinuria, n=4

Parameter, Mean (SD)	Baseline	Week 25 (EOT)	Week 37 (EOT)
UPCR (mg/mg)	**5.8 (5.1)**	**1.3 (0.5)**	**1.8 (0.7)**
eGFR (mL/min/1.73 m^2)	**122.5 (15.2)**	**122 (22.7)**	**120 (16.5)**
24-h protein excretion (g/d)	5.6 (4.1)	1.6 (1.1)	2.6 (0.6)
Serum albumin (g/dL)	3.0 (0.6)	3.7 (0.4)	3.9 (0.3)
Total cholesterol (mmol/L)	6.1 (1.4)	5.6 (0.9)	5.1 (0.3)
Triglyceride (mmol/L)	2.1 (0.6)	2.1 (0.9)	1.6 (0.4)
Daily CS dose (mg/d)	19.8 (20.2)	8.3 (2.4)	8.0 2.4)

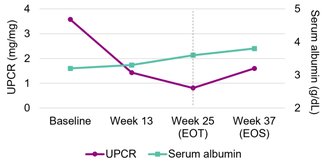
FIGURE 2: Zetomipzomib Treatment Improved UPCR, Serum Albumin Levels and SLEDAI-2K scores in Patients with Nephrotic Range Proteinuria, n=4

Patient A (Class IV)



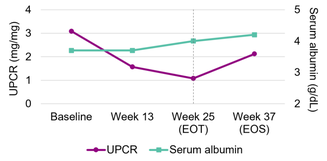
	Baseline	Week 25 (EOT)	Week 37 (EOS)
SLEDAI-2K	10	8	8

Patient B (Class III)



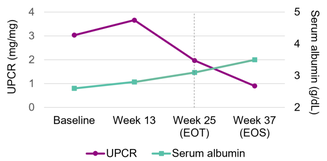
	Baseline	Week 25 (EOT)	Week 37 (EOS)
SLEDAI-2K	18	8	10

Patient C (Class IV)



	Baseline	Week 25 (EOT)	Week 37 (EOS)
SLEDAI-2K	10	4	8

Patient D (Class III+V)



	Baseline	Week 25 (EOT)	Week 37 (EOS)
SLEDAI-2K	20	12	8

Normal serum albumin reference range: 3.5 to 5.5 g/dL.

TABLE 3: Improvements in Key Serologic Biomarkers Observed in Nephrotic Range Patients with Abnormal Levels at Baseline, n=4

Biomarker	Patients with Abnormal Levels at Baseline	Week 25 (EOT)		Week 37 (EOS)	
		Patients with Improvement	Patients with Normalization	Patients with Improvement	Patients with Normalization
Anti-dsDNA	4	3	2	2	1
C3	3	3	2	3	1
C4	1	1	1	1	1

Reference ranges: anti-dsDNA, <20 IU/mL; C3, 90-180 mg/dL; C4, 10-40 mg/dL.

TABLE 4: Zetomipzomib Demonstrated A Favorable Safety and Tolerability Profile

Adverse Events	Zetomipzomib n=4 n (%)	Zetomipzomib N=21 n (%)
Patients with at least 1 TEAE	4 (100)	21 (100)
Most common TEAE: injection-site reaction	3 (75)	15 (71.4)
TEAE leading to study drug discontinuation	0 (0)	4 (19.0)[a]
Grade 3 TEAE	0 (0)	6 (28.6)
Serious TEAE	0 (0)	2 (9.5)[b]
Grade ≥3 Infectious TEAE	0 (0)	0 (0)
Opportunistic Infections	0 (0)	0 (0)
Death	0 (0)	0 (0)

No Grade 4 TEAE was reported. *[a] Three related TEAEs (injection site infiltration, asthenia, reticulocyte increase) and 1 unrelated serious TEAE (worsening pulmonary arterial hypertension [PAH] with acute kidney injury [AKI] and urinary tract infection [UTI]) led to study drug discontinuation. Patient subsequently had SAEs of AKI and UTI (unrelated) and has recovered. [b] One related serious TEAE of acute protracted migraine was reported. Study drug was temporarily interrupted, and patient has recovered and completed the study.*
Data shown for n=4 nephrotic range proteinuria patients and N=21 patients enrolled in protocol Amendment 4 who received ≥1 dose of zetomipzomib.

CONCLUSIONS

In this post-hoc analysis of patients with nephrotic range proteinuria from the MISSION Phase 2 study, zetomipzomib 60 mg SC QW treatment demonstrated:

- Clinically meaningful improvement in UPCR as early as Week 13 in patients with persistent proteinuria despite stable SOC
- Improvement/normalization of serum albumin levels and key serologic biomarkers in those with abnormal values at baseline
- Favorable safety and tolerability profile without evidence of immunosuppression (no serious/opportunistic infections)
- Potential to be a long-term, steroid-sparing immunomodulatory treatment for hard-to-treat LN patients

A larger placebo-controlled Phase 2b trial (PALIZADE; NCT05781750; KZR-616-202) has been initiated to evaluate the efficacy and safety of zetomipzomib in LN

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CONTACT INFORMATION

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Abbreviations: ACE, angiotensin-converting enzyme, AKI, acute kidney injury; anti-dsDNA, anti-double stranded DNA; ARB, angiotensin II receptor antagonists; CRR, complete renal response; eGFR, estimated glomerular filtration rate; EOS, end of study; EOT, end of treatment; LN, lupus nephritis; ORR, overall renal response; PAH, pulmonary arterial hypertension; SAE, serious adverse event; SLE, systemic lupus erythematosus; SOC, standard of care; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.