Zetomipzomib (KZR-616), A First-in-Class, Selective Immunoproteasome Inhibitor, Achieved Clinically Meaningful Renal Responses in Refractory or Hard-To-Treat Patients With Lupus Nephritis: Completed Phase 2 MISSION Study Results

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Submitted on behalf of the MISSION (KZR-616-002) Phase 2 Investigators

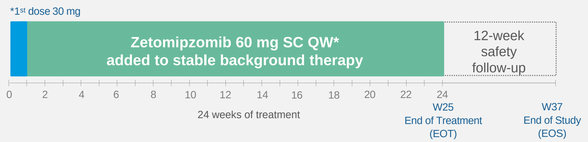
Introduction

- Zetomipzomib, a first-in-class, selective inhibitor of immunoproteasome, is active in a murine model of systemic lupus erythematosus (SLE)/lupus nephritis (LN)[1]
- In the NZB/W murine model of SLE/LN, zetomipzomib treatment prevented renal damage and reduced expression of genes associated with tissue damage in the glomerulus and tubulointerstitium[1]
- The MISSION Phase 1b/2, open-label study (NCT03393013; KZR-616-002) evaluated safety, tolerability, and exploratory efficacy of zetomipzomib in patients with SLE +/- LN.
- In the Phase 1b portion, zetomipzomib was well-tolerated in patients with active SLE +/- LN and resulted in improvement across disease activity measures as well as biomarkers, including reduced proteinuria and urinary CD163 (uCD163) in 2 of 2 patients with LN[2]
- Results from the completed Phase 2 portion of the MISSION study are presented

Methods

- The Phase 2 portion of the study 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 24-hour urine protein to creatinine ratios (UPCR) ≥1.0 mg/mg despite stable background therapy with corticosteroids and at least one immunosuppressive for ≥8 weeks
- 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, UPCR, renal response parameters, renal function, SLE disease activity and biomarkers were measured
- 24-hour uCD163 was measured as an exploratory endpoint in 13 patients

Figure 1. **Study Design for Phase 2 of the MISSION Study**



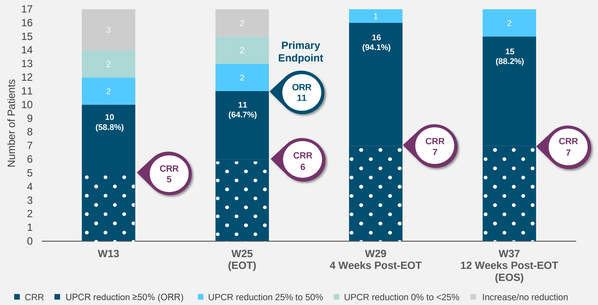
Patients in MISSION Phase 2 did not receive standard LN induction therapy and steroid taper was not protocol-mandated

Results

- 21 patients received ≥1 dose of zetomipzomib (safety population) and 4 patients discontinued before end of treatment (evaluable population, n=17)
- 90.5% were women with a mean age of 35.3 years; 52.4% were Hispanic/Latino
- Patients had mean durations of SLE (9.7 years) and LN (5.3 years) with mean 24-hour UPCR of 2.6 mg/mg and mean eGFR of 104.7 mL/min/1.73 m^2
- Histology: Class III 28.6%; Class IV 52.4%; Class III+V 14.3%; Class IV+V 4.8%
- A kidney biopsy was performed in 14.3% within 12-24 months, 23.8% within 6-12 months, and 61.9% within 6 months of screening or during screening to confirm eligibility
- Concomitant medications included corticosteroids (100%; mean dose: 20.2 mg/d), MMF or mycophenolic acid (95.2%), HCQ (66.7%), and AZA (9.5%)

Results (cont'd)

Figure 2. **Zetomipzomib Treatment Demonstrated Clinically Meaningful Renal Responses With Additional ORR*s and CRR†s Observed Through W37 (n=17)**



*ORR: ≥50% reduction in UPCR compared to baseline †CRR: UPCR ≤0.5, eGFR ≥60 mL/min/1.73m^2 or no worsening of eGFR from baseline of ≥25%, prednisone (or equivalent) ≤10 mg and no use of prohibited medication

Figure 3. **Zetomipzomib Treatment Achieved 57% and 83% Reduction in Median UPCR at W25 and W37, Respectively (n=17)**

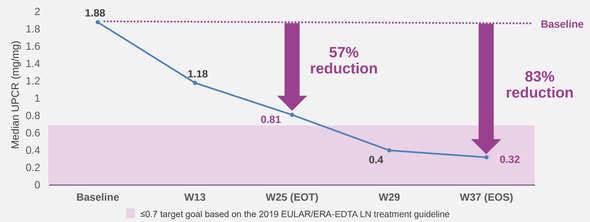


Table 1. **Zetomipzomib Treatment Achieved UPCR Targets Recommended by the 2019 EULAR/ERA-EDTA Lupus Nephritis Treatment Guideline Within 6 Months (n=17)**

2019 EULAR/ERA-EDTA Guideline[3] UPCR Treatment Targets	Zetomipzomib n (%)	Time Point in MISSION Study
≥25% reduction in UPCR by 3 months	12 (70.6)	W13
≥50% reduction in UPCR by 6 months	11 (64.7)	W25 (EOT)
UPCR ≤0.7 mg/mg by 12 months		
UPCR ≤0.7 at 6 months in MISSION study	6 (35.3)	W25 (EOT)
UPCR ≤0.7 at 9 months in MISSION study	12 (70.6)	W37 (EOS)

Table 2. **Zetomipzomib Treatment Resulted in Consistent Treatment Benefit Across LN Biopsy Classes (n=17)**

Measure	Overall	Pure Class III	Pure Class IV	Class III/IV ± V
ORR at W25	64.7% (11/17)	60% (3/5)	70% (7/10)	50% (1/2)
CRR at W25	35.3% (6/17)	40% (2/5)	40% (4/10)	0% (0/2)

Results (cont'd)

Figure 4. **eGFR Remained Stable During the 6 Months of Zetomipzomib Treatment and the Post Treatment Period (n=17)**

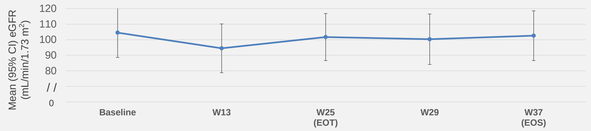
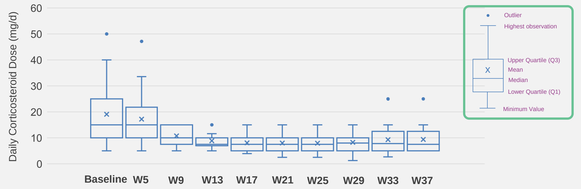


Figure 5. **By Week 13, 82.4% (14/17) of Patients Achieved a Daily Corticosteroid Dose of ≤10 mg (n=17)**



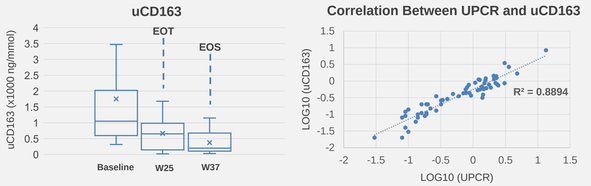
Other background immunosuppressive doses remained stable throughout the study.

Table 3. **Zetomipzomib Treatment Improved Key SLE Clinical Disease Activity Scores (A) and Serologic Biomarkers (B)**

Table 3A	Baseline Mean (SD)	Week 25 (EOT) Mean (SD)	Week 37 (EOS) Mean (SD)
SLEDAI-2K	11.3 (4.5)	6.5 (3.1)	5.8 (3.2)
PhGA	57.2 (21.7)	23.9 (19.2)	16.2 (16.6)
PtGA	23.6 (21.1)	10.7 (12.2)	6.6 (9.5)

Table 3B	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	12	10	5	9	3
C3	5	4	2	3	1
C4	4	3	2	2	2

Figure 6. **Zetomipzomib Treatment Decreased Urinary CD163*, an Inflammatory Marker Shown to Correlate With UPCR (n=13†)**



*CD163 is a transmembrane protein mainly expressed by M2c macrophages that infiltrate tissues during the "healing phase" of inflammation[4]. uCD163 was normalized to the urine creatinine for analysis. †13/17 evaluable patients consented to urine biomarker analysis.

Results (cont'd)

Table 4. **Zetomipzomib Demonstrated Favorable Safety and Tolerability Profile (Safety Population, n=21)**

Adverse Events	Zetomipzomib n (%)
Most common TEAE: injection-site reaction	15 (71.4)
TEAE leading to study drug discontinuation†	4 (19.0)
Grade 3 TEAE	6 (28.6)
Serious TEAE‡	2 (9.5)
Grade ≥3 Infectious TEAE	0 (0)
Opportunistic Infections	0 (0)
Death	0 (0)

No Grade 4 TEAE was reported. †3 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. ‡1 related serious TEAE of acute protracted migraine was reported. Study drug was temporarily interrupted, and patient has recovered and completed the study.

Summary

Treatment with zetomipzomib 60 mg SC QW for 24 weeks added to stable background LN therapy without standard induction therapy resulted in:

- UPCR reduction ≥50% in 64.7% of patients (primary endpoint) and CRR in 35%, with reduction in corticosteroids while other background meds remained stable
- Consistent renal responses regardless of LN class histology
- Preservation of renal function during the study as evidenced by stable eGFR
- Improvements in key SLE clinical disease activity scores and serologic biomarkers (anti-dsDNA, C3 and C4)
- Decrease in uCD163 levels, which were elevated at baseline and demonstrated a correlation with UPCR
- Generally mild to moderate TEAEs (Grade 1/2) without evidence of immunosuppression (no serious/opportunistic infections or immune cell depletion)
- Achievement of UPCR targets earlier than recommended by the 2019 EULAR/ERA-EDTA LN treatment guideline

Conclusions

The MISSION Phase 2 study demonstrated:

- A strong activity of zetomipzomib in LN as evidenced by reduction in UPCR, earlier achievement of EULAR/ERA-EDTA UPCR targets, and preservation of renal function
- Anti-inflammatory potential as demonstrated by reduction in uCD163, which was strongly correlated with UPCR improvement
- Potential to be a long-term, steroid-sparing, immunomodulatory LN treatment that can help refractory patients achieve their proteinuria treatment targets

References

1. Muchamuel et al. 2019 ACR/ARP Annual Meeting. **2**. Furie et al. EULAR 2021 Virtual Congress. **3**. Fanouriakis et al. *Ann Rheum Dis*. 2020;79(6):713-723. **4.** Mejia-ViletJ, et al. *JASN*. 2020;31(6):1335-1347.

Author Disclosures and Acknowledgements

SVP is a consultant for Alexion, Aurinia, BMS, GSK, Kezar, and received a grant/research grant from Aurinia, EMD-Serono, and NIH-NIDDK. **RF** is a consultant for AstraZeneca and Biogen. **AS** is an advisor for AstraZeneca, BMS, Eli Lilly, GSK, and Kezar. **SYH, LL,** and **NRH** are employees and shareholders of Kezar. **RLL** is a consultant and shareholder of Kezar.
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Abbreviations: CRR, complete renal response; eGFR, estimated glomerular filtration rate; EOS, end of study; EOT, end of treatment; LN, lupus nephritis; ORR, overall renal response; PhGA, Physician Global Assessment; PtGA, Patient Global Assessment; QW, once weekly; SC, subcutaneous; SD; standard deviation; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; TEAE, treatment-emergent adverse event; uCD163, urinary CD163; UPCR, urine protein to creatinine ratio.

TH-PO487 • Presented at ASN Kidney Week 2022 • Orlando, FL, USA • November 3, 2022

We thank all the MISSION investigators, site personnel and patients for participating in this trial.