Zetomipzomib (KZR-616), A First-in-Class, Selective Immunoproteasome Inhibitor for the Treatment of Lupus Nephritis: Results from the Completed Phase 2 Portion of the MISSION Study

Amit Saxena, MD[1]; Samir V. Parikh, MD[2]; Richard Furie, MD[3]; Richard L. Leff, MD[4]; Steven Y. Hua, PhD[4]; Li Long, MD[4]; R. Andrea Fan, PhD[4]. Noreen R. Henig, MD[4]

[1]NYU School of Medicine, New York, NY, USA; [2]The Ohio State University, Columbus, OH, USA; [3]Northwell Health, Great Neck, NY, USA; [4]Kezar Life Sciences, South San Francisco, CA, USA

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

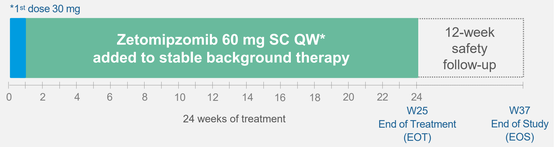
Introduction

- Zetomipzomib is a first-in-class, selective inhibitor of the immunoproteasome
- When immunoproteasomes are selectively inhibited, multiple pathways involved in inflammatory cytokine production and immune effector cell activity – including macrophages, B cells and T cells – are also inhibited, leading to broad immunomodulation across both the innate and adaptive immune systems[1-3]
- 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[4]
- 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 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 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**



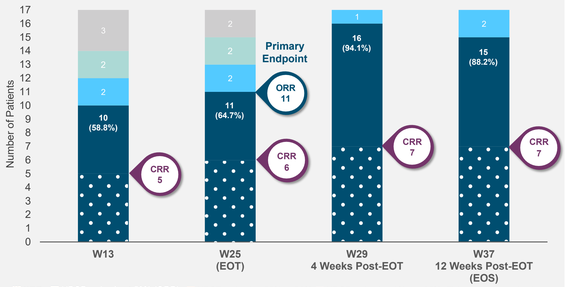
Patients in MISSION Phase 2 did not receive standard LN induction therapy and steroid taper was not protocol-mandated

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
- 28.6% had ISN/RPS Class III, 52.4% had Class IV, 14.3% had mixed Class III+V, and 4.8% had mixed Class IV+V
- A kidney biopsy was performed in 61.9% within 6 months, 23.8% within 6-12 months, and 14.3% within 12-24 months of baseline
- Concomitant medications included corticosteroids (100%; mean dose: 20.2 mg/d), MMF or mycophenolic acid (95.2%), HCQ (66.7%), and/or AZA (9.5%)

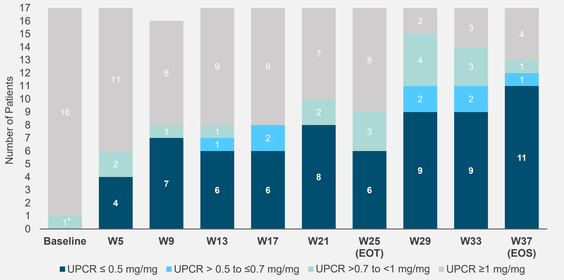
Results (cont'd)

Figure 2. **Zetomipzomib Treatment Demonstrated Clinically Meaningful Renal Response With Additional ORRs and CRRs Observed Through W37 (Evaluable Population, n=17)**



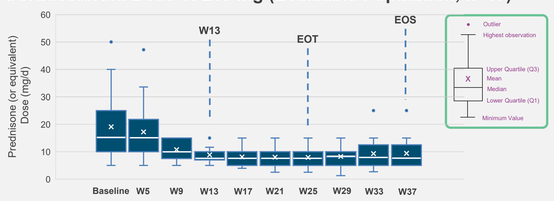
*ORR: ≥50% reduction in UPCR compared to baseline †CRR: UPCR ≤0.5, eGFR ≥60 mL/min/1.73m^2 or no worsening of eGFR from baseline of ≥25%, prednisone (or equivalent) ≤10 mg and no use of prohibited medication

Figure 3. **UPCR ≤0.5 Was Achieved by 64.7% (11/17) of Patients by End of Study at Week 37 (Evaluable Population, n=17)**



*Per protocol, patients with baseline UPCR ≥1 were included in this study. One patient had screening values >1 but W1 pre-dose UPCR was <1. The baseline UPCR value is the average of screening values and W1 pre-dose UPCR values.

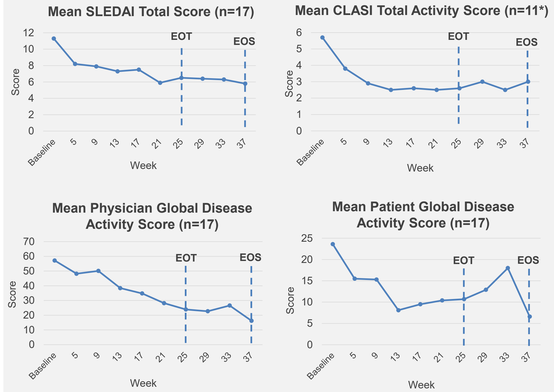
Figure 4. **By Week 13, 82.4% (14/17) of Patients Achieved a Daily Corticosteroid Dose of ≤10 mg (Evaluable Population, n=17)**



Other background immunosuppressive doses remained stable throughout the study.

Results (cont'd)

Figure 5. **Zetomipzomib Treatment Improved Key SLE Clinical Disease Activity Scores in the Phase 2 MISSION Study**

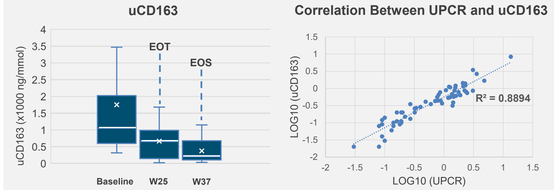


*11 patients had active cutaneous SLE at baseline (CLASI-A >0). There were 5 patients with tender joint count >0 at baseline and 1 patient with swelling joint count >0 at baseline. Improvements in tender/swollen joint counts were also observed at EOT with a slow recrudescence of scores during the post-treatment period.

Table 1. **Improvements in Key Serologic Biomarkers Were Seen in Those With Elevated Levels at Baseline**

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	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[5]. uCD163 was normalized to the urine creatinine for analysis. †13/17 evaluable patients consented to urine biomarker analysis.

Results (cont'd)

Table 2. **Zetomipzomib Demonstrated a Favorable Safety and Tolerability Profile in the Ph 2 MISSION Study (Safety Population)**

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

- Clinically meaningful ORR in 65% and CRR in 35% of patients at W25 (EOT)
- Renal response as early as Week 13 (ORR in 58.8% and CRR in 29.4%)
- Sustained renal response with additional ORRs/CRRs observed through W37
- Achievement of UPCR ≤0.5 in 64.7% of patients at W37 (EOS)
- Reduction of daily steroid dose to ≤10 mg/d in 82.4% of patients by W25 (EOT)
- Improvements in key SLE clinical disease activity scores and biomarkers
- Stable mean eGFR during the study (data not shown)
- Generally mild to moderate TEAEs (Grade 1/2)
- No evidence of immunosuppression (no serious/opportunistic infections or immune cell depletion)

Conclusions

The MISSION Phase 2 study demonstrated:

- **A strong activity of zetomipzomib in LN as evidenced by improvement in UPCR, an objective endpoint of proteinuria**
- **Anti-inflammatory potential as evidenced by a slow recrudescence in SLE clinical disease activity scores after discontinuation of zetomipzomib and improvement in uCD163 with zetomipzomib treatment**
- **Potential to be a long-term, steroid-sparing, immunomodulatory treatment for patients with LN**

References

1. Muchamuel et al. *Nat Med*. 2009;15(7):781-7. **2**. Ichikawa et al. *Arthritis Rheum*. 2012;64(2):493-503. **3**. Kalim et al. *J Immunol*. 2012;189(8):4182-93. **4**. Furie et al. EULAR 2021 Virtual Congress. **5**. Mejia-ViletJ, et al. *JASN*. 2020;31(6):1335-1347.

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Abbreviations: AKI, acute kidney injury; CLASI-A, Cutaneous Lupus Erythematosus Severity Index-Activity; 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; QW, once weekly; SAE, serious adverse event; SC, subcutaneous; 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; UTI, urinary tract infection.

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