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Zetomipzomib (KZR-616) Demonstrates Clinically Meaningful Renal Responses in Patients with Lupus Nephritis (LN): Results from the Phase 2 MISSION Study

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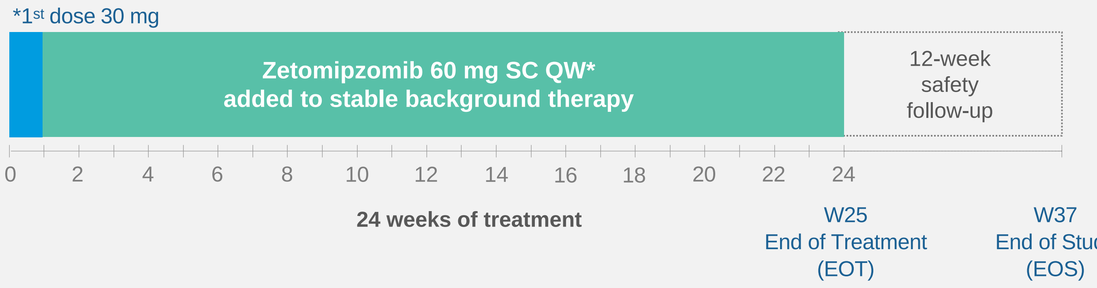
Background/purpose

- 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
- The MISSION Phase 1b/2, open-label study (NCT03393013; KZR-616-002) evaluated safety, tolerability, and exploratory efficacy of zetomipzomib in patients with systemic lupus erythematosus (SLE) +/- lupus nephritis (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
- Complete results from the MISSION Phase 2 study including post-hoc subgroup analyses are presented here

Methods

- The MISSION Phase 2 study evaluated zetomipzomib 60 mg subcutaneously once weekly for 24 weeks (1st dose: 30 mg) in patients with active LN (Class III or IV ± Class V) with urine protein to creatinine ratio (UPCR) ≥1 despite stable background therapy
- The primary endpoint was the number of patients with a 50% reduction in UPCR from baseline after 24 weeks of treatment
- Safety, tolerability, UPCR, renal response parameters, renal function, SLE disease activity and biomarkers were measured
- Post-hoc analyses of data by LN biopsy class and in patients with nephrotic range proteinuria were performed. 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*. Study Design for the MISSION Phase 2 Study**



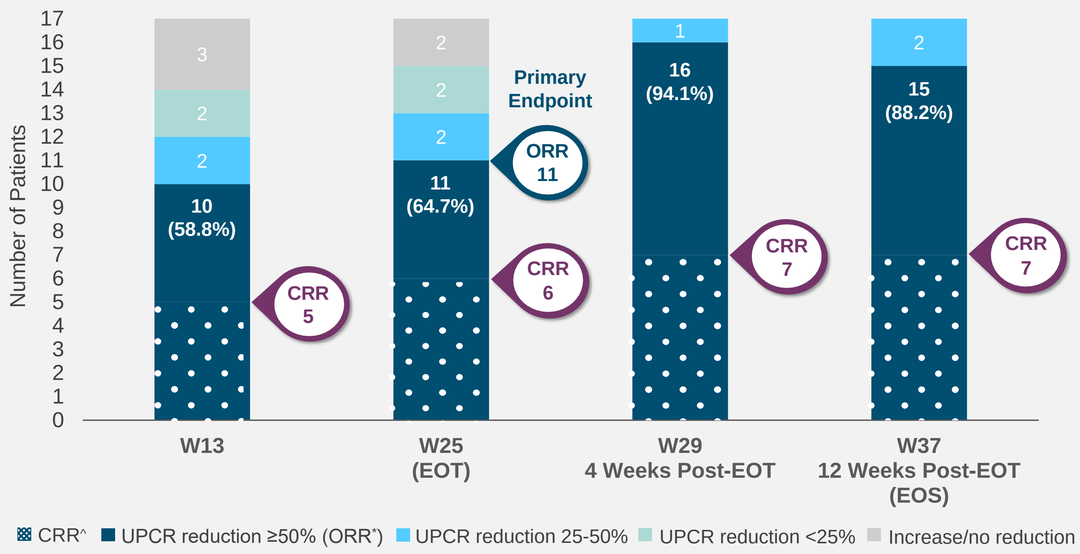
Patients in MISSION Phase 2 did not receive standard LN induction therapy and steroid taper was not protocol-mandated

Results

Key Demographic/Baseline Characteristics (Safety Population, N=21)

- 21 patients received ≥1 dose of zetomipzomib (safety population in protocol amendment 4) and 4 patients discontinued before end of treatment (evaluable population, n=17)
- Histology: Class III 28.6%; Class IV 52.4%; Class III+V 14.3%; Class IV+V 4.8%
- 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
- 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 screening
- Concomitant medications included corticosteroids (100%; mean dose: 18.8 mg/d), mycophenolate mofetil or mycophenolic acid (95.2%), hydroxychloroquine (66.7%), and azathioprine (9.5%)

***Figure 2*. Zetomipzomib Treatment Demonstrated Clinically Meaningful Renal Responses With Additional ORR*s and CRR^s 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

Results (cont'd)

***Table 1*. In the Post-hoc Subgroup Analyses, Consistent Renal Responses and Steroid-Sparing Potential Were Observed Across All LN Biopsy Classes and in Patients With Nephrotic Range Proteinuria at Baseline**

	Overall MISSION Ph 2 Evaluable Population n=17	Post-hoc Analysis by LN Biopsy Class			Post-hoc Analysis in Patients with Nephrotic Range Proteinuria n=4
		Pure Class III n=5	Pure Class IV n=10	Class III/IV+V n=2	
ORR, n (%)					
Week 25 (EOT)	11 (64.7)	3 (60.0)	7 (70.0)	1 (50.0)	3 (75)
Week 37 (EOS)	15 (88.2)	5 (100.0)	8 (80.0)	2 (100.0)	3 (75)
CRR, n (%)					
Week 25 (EOT)	6 (35.3)	2 (40.0)	4 (40.0)	0	0
Week 37 (EOS)	7 (41.2)	2 (40.0)	5 (50.0)	0	0
Mean daily steroid dose ≤10 mg					
Week 25 (EOT)	14 (82.4)	3 (60)	9 (90)	2 (100)	4 (100)
Week 37 (EOS)	13 (76.5)	3 (60)	8 (80)	2 (100)	4 (100)

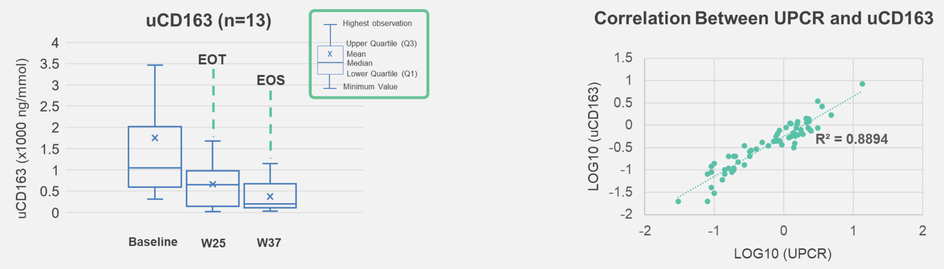
No CRR was seen in patients with nephrotic range proteinuria (UPCR ≥3.0 mg/mg at baseline) and patients with mixed Class III/IV + V group, but one patient with Class IV + V achieved CRR at Week 33.

***Table 2*. Zetomipzomib Treatment Improved Key SLE Clinical Disease Activity Scores (A) and Serologic Biomarkers (B) (Evaluable Population, n=17)**

Table 2A	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)
CLASI-A	3.7 (7.3)	1.9 (4.1)	2.1 (3.6)
TJC	1.3 (2.6)	0.1 (0.5)	0.2 (0.7)
SJC	0.1 (0.5)	0.1 (0.2)	0.2 (0.5)
PhyGA	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 2B	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 3*. 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. uCD163 was normalized to the urine creatinine for analysis. †13/17 evaluable patients consented to urine biomarker analysis.

***Table 3*. Zetomipzomib Demonstrated a Favorable Safety and Tolerability Profile Without Evidence of Direct Immunosuppression (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.

Conclusion

- **In the open-label MISSION Phase 2 study, zetomipzomib 60 mg SC QW demonstrated strong activity against LN as evidenced by improvement in UPCR and other efficacy endpoints and has the potential to be a long-term, steroid-sparing immunomodulatory treatment for LN patients**

A global, placebo-controlled Phase 2b study (PALIZADE; NCT05781750; KZR-616-202) has been initiated to continue evaluating the efficacy and safety of zetomipzomib in LN

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Abbreviations: AKI, acute kidney injury; C3, complement 3; C4, complement 4; 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; PhyGA, Physician Global Assessment; PtGA, Patient Global Assessment; QW, once weekly; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation; SJC, swelling joint count; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; TEAE, treatment-emergent adverse event; TJC, tender joint count; uCD163, urinary CD163; UPCR, urine protein to creatinine ratio; UTI, urinary tract infection; W, week.