Zetomipzomib (KZ-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 (KZ-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).
- In the NZB/W murine model of SLE/N, zetomipzomib treatment prevented renal damage and reduced expression of genes associated with tissue damage in the glomerulus and tubulointerstitium.
- The MISSION Phase 1b, open-label study (NCT02393013; KZ-616-002) evaluated safety, tolerability, and exploratory efficacy of zetomipzomib in patients with SLE with or without LN.
- In the Phase 1b portion, zetomipzomib was well-tolerated in patients with active SLE and LN and resulted in improvement across disease activity measures as well as biomarkers, including reduced proteinuria and urinary CD163 (uCD163) in ≥2 of 3 patients with LN.
- 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 in 11+ active SLE patients with active proliferative LN (Class IV or V in Class V) with 24-hour urine protein to creatinine ratio (UPCR) >500 mg/mg and concurrent stable treatment with corticosteroids and at least one other immunosuppressive for ≥8 weeks.
- The primary endpoint was the number of patients with ≥20% 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.

Results

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

- 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 4.9 years (8-13 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 m².
- Histology: Class III 28%, Class IVa 52%, Class IVg 14%, Class IVf 4-8%
- Aliskire biopsy was performed in 14.3% between 24-36 months, 23.8% within 6-12 months, and 61.9% within 6 months of screening or during screening to confirm disease.
- Concomitant medications included corticosteroids (100% mean dose: 20.2 mg/d), M/P or mycophenolic acid (95.5%), methotrexate (95.5%), and AZA (9.5%).
- UPCR targets, and preservation of renal function

Conclusions

The MISSION Phase 3 study demonstrated:
- A strong activity of zetomipzomib in LN in evidenced by reduction in UPCR, earlier achievement of EULAR/ERA-Lupus Nephritis targets, and preservation of renal function.
- Anti-inflammation potential as demonstrated by reduction in uCD163, which was strongly correlated with UPCR improvement.
- Patients as a long-term, stand-alone, immunomodulatory LN treatment that can help refractory patients achieve their proteinuria targets.

References


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N/A

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