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

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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.

The MISSION Phase 2b, open-label study (NCT03305002) 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.
- 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 (17 doses; 30 mg) in adult patients with active proliferative LN (Class III or IV if Class V) with 24-hour urine protein to creatinine ratio (UPCR) ≥2.5 despite stable background therapy with corticosteroids and at least one immunosuppressive for ≥16 weeks.
- The primary endpoint was the number of patients with ≥30% reduction in UPCR from baseline after 24 weeks of treatment (Overall Renal Response [ORR]).
- Safety, tolerability, UPCR, renal response parameters, renal function, SLE, and CRPs were measured.
- 24-hour uCD163 was measured as an exploratory endpoint in 13 patients.

Results

Figure 2. Zetomipzomib Treatment Demonstrated Clinically Meaningful ORR and CRRs Observed Through W37 (Evaluable Population, n=17)

- UPCR reduction ≥50% (ORR) at Week 25 (EOT) for patients with LN

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

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

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

- Mean SLEDAI Total Score (n=17)
- Mean CLASI Total Activity Score (n=17)

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

- Mean Physician Global Disease Activity Score (n=17)
- Mean Patient Global Disease Activity Score (n=17)

Figure 4. By Week 13, 82.4% (14/17) of Patients Achieved a Daily Corticosteroid Dose of 310 mg (Evaluable Population, n=17)

- Mean Patient Global Disease Activity Score (n=17)

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

Table 3. Efficacy at W37 in the MISSION Phase 2 Study Demonstrated:

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 disease activity scores after discontinuation of zetomipzomib and improvement in CRR with zetomipzomib treatment
- Potential to be a long-term, steroid-sparing, immunosuppressive/therapy for patients with LN

References


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