Treatment of Systemic Lupus Erythematosus With the Immunoproteasome Inhibitor KZR-616: Results From the First 5 Cohorts of the MISSION Study, an Open-label Phase 1b Dose-Escalation Study

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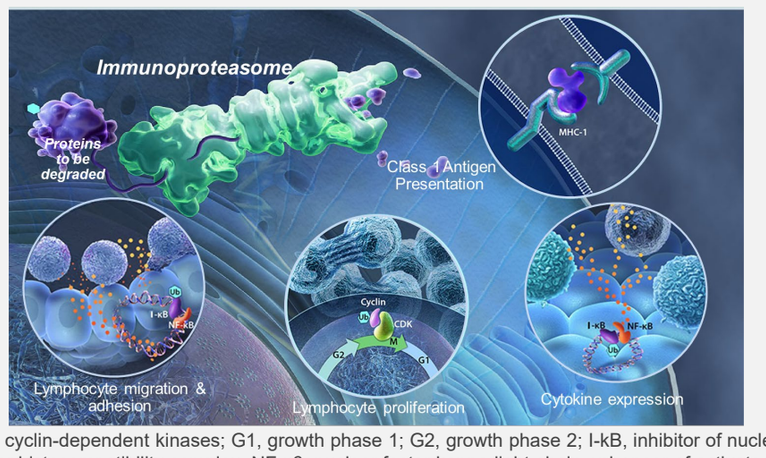
Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that can manifest with serious renal complications such as lupus nephritis (LN). Development of safer, more targeted therapies for SLE/LN is needed.[1,2] KZR-616 is a first-in-class selective immunoproteasome inhibitor in development for the treatment of severe autoimmune diseases, including LN.[3] The primary target of KZR-616 is the immunoproteasome (**Figure 1**), the form of the proteasome that is found primarily in cells of the immune system, such as lymphocytes and monocytes.[3]

Early preclinical and clinical studies support the use of KZR-616 for LN.[4,5] In murine models of SLE/LN, administration of KZR-616 was shown to prevent renal damage.[4] Complete resolution of proteinuria and reductions of autoantibody levels and renal IgG deposition were observed following KZR-616 treatment of diseased mice.[4] The MISSION study (NCT03393013) is designed to assess the efficacy, safety, and tolerability of KZR-616 in patients with SLE with or without nephritis. The preliminary results from the 1b portion of the MISSION study are presented.

Figure 1. The Immunoproteasome Is Involved in Multiple Aspects of Immune Effector Cell Function



Abbreviations: CDK, cyclin-dependent kinases; G1, growth phase 1; G2, growth phase 2; I-kB, inhibitor of nuclear factor kappa B; M, mitosis; MHC, major histocompatibility complex; NF-κβ, nuclear factor kappa-light-chain-enhancer of activated B cells; Ub, ubiquitin.

Methods

- In this 2-part ongoing multicenter study, patients received KZR-616
  - Part 1: Phase 1b, open-label multiple dose-escalation study in patients with SLE with or without nephritis
  - Part 2: Phase 2, open-label study in patients with active proliferative LN (not reported here)
- Patients in the phase 1b portion fulfilled the 2012 Systemic Lupus International Collaborating Clinics Classification Criteria and had SLE Disease Activity Index 2000 (SLEDAI-2K) ≥4 at screening, and stable background medications (eg, ≤20 mg prednisone equivalent) were required
- Patients received KZR-616 weekly subcutaneous (sc) injections at 45 mg (Cohort 1) or 60 mg (Cohort 2) for 13 weeks; those in Cohort 2a received doses of 30 mg, 30 mg, 45 mg, 45 mg, and 60 mg; those in Cohorts 2b and 2c received an initial dose of 30 mg followed by the target dose of 60 mg
- Exploratory efficacy measures and biomarkers were evaluated, including at weeks 1 (baseline), 13 (end of treatment), and 25 (end of study)
- Efficacy was assessed in patients who completed the study, with safety assessed in the safety population (patients receiving any study drug)

Results

Patient Enrollment and Demographics

- As of May 4, 2020, 39 patients were enrolled across 5 dose cohorts
  - Mean age was 52.0 years, mean SLE disease duration was 96.2 months, and 94.9% of patients were women
  - Among those taking prednisone, the average dose was 7.8 mg daily (qd)
  - 22 patients completed phase 1b of the study, and 7 patients' participation is ongoing
  - Final cohort of the phase 1b study is currently under enrollment

Disease Activity

- Mean values of all 7 measures of disease activity improved in patients who completed 13 weeks of treatment (**Table 1**)
  - These improvements were maintained or enhanced during the follow-up period

Table 1. Disease Activity Scores Over Time in Patients From Cohorts 1-2b (Study Completers, n=22)

Scores, Mean (SD)	Baseline	Week 13 (End of Treatment)	Week 25 (End of Study)
SLEDAI-2K	9.2 (2.3)	6.7 (2.6)	7.0 (2.6)
CLASI-A	5.8 (4.9)	3.5 (3.6)	3.7 (3.9)
Tender Joint Count	12.5 (6.6)	5.9 (5.1)	6.0 (4.1)
Swollen Joint Count	8.5 (6.4)	3.2 (4.2)	2.2 (2.7)
Physician Global Assessment	55.5 (23.6)	39.6 (23.1)	38.1 (18.0)
Patient Global Assessment	63.0 (21.8)	42.3 (24.7)	44.1 (19.2)
Patient Assessment of Pain	64.3 (19.3)	50.1 (24.9)	44.7 (22.9)

Abbreviations: CLASI-A, Cutaneous Lupus Erythematosus Severity Index-Activity; SD, standard deviation; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Biomarkers

- Six patients had elevated anti–dsDNA antibody levels at baseline, and of the 5 who completed 25 weeks, levels decreased with treatment (**Table 2**)

Results (cont'd)

Table 2. Anti-dsDNA Titers for Those with Elevated Levels at Baseline (Completers Through Week 25)

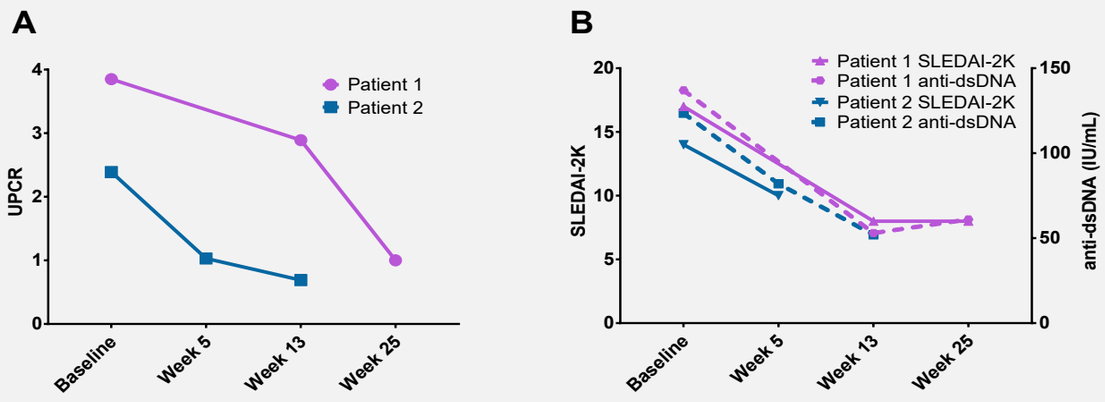
Individual	Mean Anti-dsDNA Level, IU/mL (Baseline)	% Change from Baseline, Week 13 (End of Treatment)	% Change from Baseline, Week 25 (End of Study)
Patient A	1015	–64.0	–82.0
Patient B	87	–20.7	–33.3
Patient C	32	–6.3	–18.8
Patient D	134	–60.4	–54.5
Patient E	90	–76.7	–68.9

Abbreviation: anti-dsDNA, anti double-stranded DNA antibody.

Lupus Nephritis (LN)

- Two patients in phase 1b had prior renal biopsies with acute proliferative LN resistant to best available therapy
  - Two of two patients showed a >50% reduction from baseline in proteinuria and had reductions in SLEDAI-2K and anti-dsDNA levels (**Figure 2**)
  - Patient 1 (Cohort 2a, LN class IV/V) had a baseline stable treatment regimen of leflunomide, hydroxychloroquine (HCQ), and prednisone (10 mg/day) and had failed prior tacrolimus therapy
  - Patient 2 (Cohort 2a; LN class III) had a baseline stable treatment regimen of mycophenolate mofetil (2 g), HCQ, and prednisone (10 mg/day); this patient's participation in the study is ongoing, and complete results were not available at the data cutoff

Figure 2. UPCR (A), SLEDAI-2K, and Anti-dsDNA (B) Values in 2 Patients With LN



Abbreviations: anti-dsDNA, anti double-stranded DNA antibody; LN, lupus nephritis; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR, urine protein to creatine ratio.

Safety

- Most patients had mild (87.2%) or moderate (30.8%) adverse events (AEs); the most common AEs were injection site erythema, nausea, and vomiting (**Table 3**)
  - There were no reports of peripheral neuropathy or prolonged hematologic AEs and no clinically significant laboratory abnormalities
  - Four serious AEs were reported: thrombotic microangiopathy, herpes zoster, systemic inflammatory response, and viral infection complicated by chest pain
- No discontinuations have been observed to date in later cohorts

Table 3. Safety Data (Safety Population)

		Lyophilized formulation		
Measures, No. (%)	Cohort 2a[a] (n=14)	Cohort 2b (n=6)	Cohort 2c[b] (n=6)	All Patients[c] (Cohorts 1-2c) (n=39)
Common TEAEs	12 (85.7)	4 (66.7)	5 (83.3)	34 (87.2)
Injection Site Reactions	9 (64.3)	2 (33.3)	4 (66.7)	25 (64.1)
Nausea	5 (35.7)	1 (16.7)	2 (33.3)	14 (35.9)
Vomiting	4 (28.6)	1 (16.7)	1 (16.7)	12 (30.8)
TEAEs ≥ Grade 3	2 (14.3)	1 (16.7)	0 (0.0)	4 (10.3)
Infectious TEAEs ≥ Grade 3	1 (7.1)	1 (16.7)	0 (0.0)	2 (5.1)
Infectious TEAEs; All Grades	5 (37.5)	2 (33.3)	0 (0.0)	8 (20.5)
Serious TEAEs	2 (14.3)	1 (16.7)	0 (0.0)	4 (10.3)
Any Study Discontinuation	4 (28.6)	0 (0.0)	0 (0.0)	10 (25.6)
Patients Receiving Prednisone	10 (71.4)	4 (66.7)	2 (33.3)	26 (66.7)

[a]Patients received 4 doses to reach target dose. [b]Ongoing. [c]All patients are inclusive of patients from Cohort 1 as well.

Abbreviation: TEAE, treatment-emergent adverse event.

Conclusions

- KZR-616 is a novel, first-in-class, selective immunoproteasome inhibitor with broad therapeutic potential across multiple autoimmune diseases, including LN
- Weekly KZR-616 up to 60 mg sc appears to be safe, well-tolerated and showed evidence of improving disease activity by multiple measures in patients with active SLE on stable background therapy (including 2 patients with LN) in the phase 1b portion of MISSION
- The ongoing open-label phase 2 portion of MISSION will further evaluate KZR-616 (30 mg first dose, then 60 mg once weekly sc) for the treatment of LN which incorporates a primary study endpoint defined by a ≥50% reduction in the urine protein to creatine ratio at 6 months

References

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