Treatment of SLE With or Without Nephritis With the Immunoproteasome Inhibitor KZR-616: Updated Results of the MISSION Study

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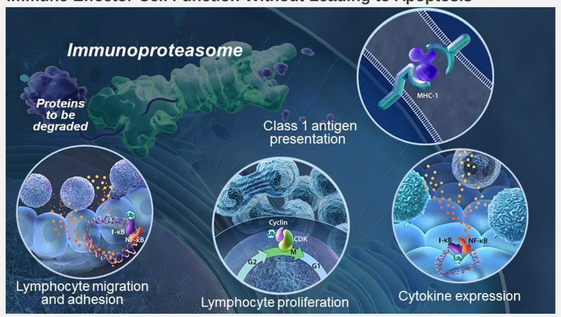
Introduction

SLE/LN and KZR-616

Systemic lupus erythematosus (SLE) is an autoimmune disease, and lupus nephritis (LN) is one of the most severe manifestations.[1,2] LN is one of the primary causes of death and disability in patients with SLE,[3] and the development of safer, more targeted therapies for SLE/LN is needed.[1,2] KZR-616 is a selective immunoproteasome inhibitor in development for the treatment of severe autoimmune diseases, including LN.[4] The primary target of KZR-616 is the immunoproteasome (**Figure 1**), found in cells of the immune system.[4] Selective targeting of the immunoproteasome by KZR-616 is expected to normalize the immune response. As the first selective immunoproteasome inhibitor to be studied in clinical trials, KZR-616 has a unique mechanism of action.[4]

Figure 1. The Immunoproteasome Is Involved in Multiple Aspects of Immune Effector Cell Function Without Leading to Apoptosis

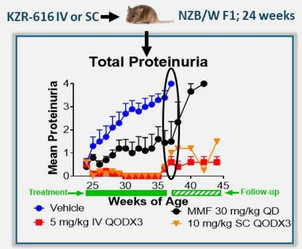


Abbreviations: CDK, cyclin-dependent kinases; G1, growth phase 1; G2, growth phase 2; I-kB, inhibitor of nuclear factor kappa B; M, mitosis; MHC, major histocompatibility complex; NF-κβ, nuclear factor kappa-light-chain-enhancer of activated B cells; Ub, ubiquitin.

Previous Studies of KZR-616

Early preclinical and clinical studies support the use of KZR-616 for LN (**Figure 2**).[5,6] In murine models of SLE/LN, administration of KZR-616 prevented renal damage through various markers.[5] The phase 1b/phase 2 MISSION study (NCT03393013) is designed to assess the safety, tolerability, and efficacy of KZR-616 in patients with SLE with or without nephritis. The phase 1b portion of MISSION is now fully enrolled; interim results through September 24, 2020, are reported here. The phase 2 portion is actively enrolling.

Figure 2. KZR-616 Blocks LN Disease Progression in NZB/W F1 Mice



Abbreviations: IV, intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; NZB/W F1, New Zealand black x New Zealand white first filial generation; QD, once a day; QODX3, every third day; SC, subcutaneous.

Methods

- In the 2-part multicenter MISSION study, patients receive KZR-616
  - Part 1: Phase 1b, open-label, multiple dose-escalation study of KZR-616 subcutaneously (SC) weekly (QW) in patients with SLE with or without nephritis
  - Part 2: Phase 2, open-label responder analysis of KZR-616 60 mg SC QW in patients with active proliferative LN (study enrolling)
  - A 12-month open-label extension study of KZR-616 60 mg SC QW with at least 1 immunosuppressive agent as a background treatment is planned

Methods (cont'd)

Phase 1b Open-Label Dose-Escalation Study

- Patient population
  - Diagnosed SLE (per Systemic Lupus International Collaboration Criteria classification criteria)
  - SLE Disease Activity Index 2000 (SLEDAI-2K) ≥4 despite stable background therapy
- Investigational therapy: KZR-616 SC QW at the following doses for 13 weeks, then follow-up for 12 weeks
  - Cohort 1: 45 mg
  - Cohort 2: 60 mg
  - Cohort 2a: 30 mg, 30 mg, 45 mg, and 45 mg, followed by target dose of 60 mg
  - Cohorts 2b and 2c: initial dose of 30 mg followed by the target dose of 60 mg (lyophilized formulation)
  - Cohort 3: initial dose of 30 mg followed by the target dose of 75 mg (lyophilized formulation)
- Additional medications
  - It was recommended that patients receive stable background medications (eg, ≤20 mg prednisone equivalent, ≤25 mg/wk methotrexate, ≤20 mg/d leflunomide)
  - In Cohorts 2c and 3 and for the first 2 doses, patients received prophylactic oral electrolyte solution, nonsedating antihistamines, and antiemetics and/or dose escalation
- Outcomes
  - Safety and tolerability were assessed throughout the study in the safety population (patients receiving any study drug)
  - Efficacy measures: evaluated throughout the study, including at weeks 1 (baseline), 13 (end of treatment), and 25 (end of study)
  - Assessed in patients in the evaluable population (ie, patients in the intention-to-treat population who did not withdraw from the study before week 13) as of September 24, 2020
- Pharmacokinetic (PK) parameters were assessed, and the pharmacodynamic (PD) parameter of proteasome activity was measured with a subunit active site binding assay (ProCISE)[7]

Results

Patient Enrollment and Demographics

- Phase 1b: As of September 24, 2020, the study is fully enrolled, with 47 patients in 6 cohorts
  - 33 patients have completed treatment, and 28 have completed the study, including 2 patients with active, biopsy-proven proliferative LN
  - Mean age was 51.0 (standard deviation [SD], 13.3) years, mean SLE disease duration was 110.5 (SD, 142.2) months, and 95.7% of patients were women
  - Concomitant medications most commonly used among patients included hydroxychloroquine (HCQ; n=34, 73.9%), prednisone (n=30, 65.2%), paracetamol (n=16, 34.8%), folic acid (n=14, 30.4%), and ondansetron (n=10, 21.7%)
  - Among those taking prednisone, the average dose was 8.4 (SD, 4.2) mg/d
  - Cohort 3 (75-mg dose, final cohort of the phase 1b portion) is fully enrolled as of September 2020

Safety

- 38 patients (82.6%) have reported adverse events (AEs); the most common AEs were injection-site erythema, nausea, and vomiting (**Table 1**)
  - There were no reports of peripheral neuropathy or prolonged hematologic AEs and no clinically significant laboratory abnormalities
- Four serious AEs were reported in 4 patients: 1 case each of thrombotic microangiopathy, herpes zoster, systemic inflammatory response syndrome, and viral infection complicated by chest pain

Disease Activity

- Mean values of all 7 measures of disease activity improved in evaluable patients (**Table 2**)
  - These improvements were generally maintained or enhanced during the follow-up period, as indicated by similar or lower scores at week 25 than at baseline

Biomarkers

- Among patients who completed the phase 1b study, 7 had elevated anti–double-stranded DNA antibody (anti-dsDNA) levels at baseline, and these levels decreased in all patients with treatment. In 3 of the 7 patients, anti-dsDNA levels were reduced by >50% (**Table 3**)

Results (cont'd)

Table 1. Safety Data, With Improved Tolerability in Later Cohorts (Safety Population)

Measures, No. (%)	Cohort 2a[a] (n=14)	Cohort 2b (n=6)	Cohort 2c (n=8)	All patients[b] (Cohorts 1-3) (N=46)
At least 1 TEAE	12 (85.7)	4 (66.7)	7 (87.5)	38 (82.6)
Most common TEAEs				
Injection-site erythema	5 (35.7)	2 (33.3)	6 (75.0)	20 (43.5)
Nausea	5 (35.7)	1 (16.7)	4 (50.0)	18 (39.1)
Vomiting	4 (28.6)	1 (16.7)	2 (25.0)	14 (30.4)
TEAEs ≥ grade 3	3 (21.4)	0 (0.0)	0 (0.0)	4 (10.3)
Infectious TEAEs ≥ grade 3	1 (7.1)	0 (0.0)	0 (0.0)	1 (2.2)
Infectious TEAEs; all grades	5 (37.5)	2 (33.3)	2 (25.0)	10 (21.7)
Serious TEAEs	2 (14.3)	1 (16.7)	0 (0.0)	4 (8.7)
TEAEs leading to d/c of study drug	2 (14.3)	0 (0.0)	0 (0.0)	10 (21.7)
Patients receiving prednisone	10 (71.4)	4 (66.7)	5 (62.5)	30 (65.2)

[a]Patients received 4 doses to reach target dose. [b]All patients are inclusive of patients from Cohort 1. 47 patients completed enrollment, but data for one patient were not entered at time of data cut.
Cohorts 2b and 2c (as well as 3, data not presented) received a lyophilized formulation of KZR-616, prophylactic oral electrolyte solution, nonsedating antihistamines, and antiemetics and/or dose escalation
Abbreviations: d/c, discontinuation; TEAE, treatment-emergent adverse event.

Table 2. Mean Disease Activity Scores Decreased Over Time With KZR-616 Treatment

Instrument	Baseline		Week 13 (end of treatment)		Week 25 (end of study)	
	n[a]	Mean (SD)	n[a]	Mean (SD)	n[a]	Mean (SD)
SLEDAI-2K	33	9.2 (2.7)	31	6.7 (2.3)	27	7.2 (2.4)
CLASI-A	32	5.0 (4.5)	32	2.9 (3.4)	27	3.4 (3.7)
TJC	33	11.2 (6.4)	32	5.0 (4.8)	27	5.6 (3.9)
SJC	33	7.7 (5.7)	32	2.5 (3.8)	27	2.1 (2.6)
PhysGA	33	57.0 (22.2)	32	40.4 (23.7)	27	39.6 (17.1)
PtGA	33	59.3 (23.0)	32	37.8 (24.9)	27	44.7 (20.3)
HAQ-pain	33	59.3 (21.4)	32	44.2 (26.6)	27	44.6 (23.8)

[a]Not all completing patients were evaluable because data had not been entered at the time of the data cut.
Abbreviations: CLASI-A, Cutaneous Lupus Erythematosus Severity Index-Activity; HAQ, Health Assessment Questionnaire; PhysGA, Physician Global Assessment; PtGA, Patient Global Assessment; SD, standard deviation; SJC, swollen joint count; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; TJC, tender joint count.

Table 3. Anti-dsDNA Antibody Titers Reduced Over Time for KZR-616 Treatment in 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[a]	87	−20.7	−33.3
Patient C	32	−6.3	−18.8
Patient D[b]	134	−60.4	−54.5
Patient E[a]	90	−76.7	−68.9
Patient F[b]	98	−46.9	−45.9
Patient G	29	−17.2	−24.1

[a]History of nephritis. [b]Active nephritis.
Abbreviation: anti-dsDNA, anti–double-stranded DNA antibody.

Results (cont'd)

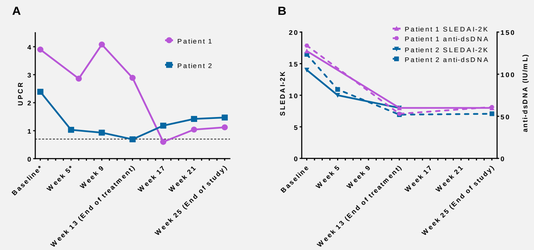
Pharmacokinetics/Pharmacodynamics

- PK: As previously reported, SC bioavailability was ~100%; drug exposure increased dose proportionally with rapid absorption (T_{max}, 15-30 minutes) and clearance ($T_{1/2}$, ~2 hours)[7]
- PD: KZR-616 45 or 60 mg SC QW selectively inhibits the immunoproteasome[9]

Lupus Nephritis

- Two patients in phase 1b had prior renal biopsies with acute proliferative LN resistant to best available therapy
  - Patient 1 (Cohort 2a, LN class IV/V) had a baseline stable treatment regimen of leflunomide, HCQ, and prednisone (10 mg/d), and prior tacrolimus therapy had failed
  - Patient 2 (Cohort 2c; LN class III) had a baseline stable treatment regimen of mycophenolate mofetil (2 g), HCQ, and prednisone (10 mg/d)
- These 2 patients were the only patients in the phase 1b study with baseline urine protein to creatinine ratio (UPCR) >1; 2 of 2 patients showed a >50% reduction from baseline in proteinuria (UPCR) (**Figure 3A**) and had reductions in SLEDAI-2K and anti-dsDNA levels (**Figure 3B**)

Figure 3. Improvements in UPCR (A), SLEDAI-2K, and Anti-dsDNA (B) Over Time With KZR-616 in 2 Patients With LN



*Corrections: spot UPCR values at baseline and week 5 for patient 1 were 3.38 and 2.08, respectively, and were presented on the ACR Convergence website.
Dotted line in A indicates a 0.7 UPCR threshold.
Abbreviations: anti-dsDNA, anti–double-stranded DNA antibody; LN, lupus nephritis; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR, urine protein to creatinine ratio.

Conclusions

- KZR-616 is a novel, first-in-class, selective immunoproteasome inhibitor with broad therapeutic potential across autoimmune diseases, including LN
- Results from the phase 1b portion of MISSION indicate that KZR-616 60 mg SC QW is well positioned as a long-term treatment option in severe autoimmune diseases
  - Weekly administration of KZR-616 appears to be safe, and improved tolerability was seen with a dose step-up strategy, use of lyophilized formulation, and use of select premedications
  - KZR-616 is associated with improvements in multiple exploratory efficacy endpoints and normalization of expression of key erythrocyte genes[8]
- Two of two patients with LN showed a >50% reduction from baseline in proteinuria and had reductions in SLEDAI-2K and anti-dsDNA levels with KZR-616
- The ongoing open-label phase 2 portion of MISSION will further evaluate KZR-616 for the treatment of LN, with a primary study endpoint defined by the number of patients with a ≥50% reduction in the UPCR at 6 months

References

1. Tamirou F, et al. *RMD Open*. 2018;4(2):e000793. 2. Dall'Era M. *Curr Opin Rheumatol*. 2017;29(3):241-247. 3. Institute for Clinical and Economic Review. Accessed October 6, 2020. https://icer-review.org/wp-content/uploads/2020/08/ICER_Lupus-Nephritis_Revised-Scope_092920.pdf 4. Xi J, et al. *Eur J Med Chem*. 2019;182:111646. 5. Muchamuel T, et al. *Ann Rheum Dis*. 2018;77(suppl 2):685. 6. Snyder B, et al. Presented at: ACR/ARP Annual Meeting; Nov 8-13, 2019; Atlanta, GA. 7. Lickliter J, et al. *Arthritis Rheumatol*. 2017; 69(suppl 10):3639. 8. Fan RA, et al. Presented at: ACR/ARP Annual Meeting; November 8-13, 2019; Atlanta, GA. 9. Chaussabel D, et al. *Immunity*. 2008;29(1):150-164.

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Three data corrections appear here as compared with the poster that appears on the ACR website (ACR Convergence 2020). The corrections do not change the overall interpretation of the data.