KZR-616, A Selective Immunoproteasome Inhibitor for the Treatment of Systemic Lupus Erythematosus: Results From the Completed Dose Escalation Phase 1b Portion of the MISSION Study

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Richard Furie, MD[1]; Samir V. Parikh, MD[2]; Jinhai Wang, PhD[3]; Darrin Bomba[3]; Richard L. Leff, MD[3]; Christopher Kirk, PhD[3]; Andrea Fan, PhD[3]; Noreen Roth Henig, MD[3]

[1]Northwell Health, Great Neck, NY, USA; [2]The Ohio State University Wexner Medical Center, Columbus, OH, USA; [3]Kezar Life Sciences, South San Francisco, CA, USA

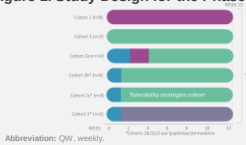
Introduction

- KZR-616 is a first-in-class selective inhibitor of the immunoproteasome, which is active in autoimmune disease models, including murine models of systemic lupus erythematosus (SLE)/lupus nephritis (LN)[1,2,3]
  - The immunoproteasome is found exclusively in immune effector cells, but expression is induced in inflamed tissues
  - KZR-616 leads to immunomodulation but not induction of immunosuppression in preclinical models[4]
- KZR-616 was well tolerated in 2 healthy volunteer studies in a total of 100 participants receiving up to 75 mg subcutaneously (SC); >80% immunoproteasome inhibition levels were observed at doses ≥30 mg[3,5,6]
- Reduction in proteinuria, as measured by urine to protein creatinine ratio (UPCR), is a robust predictor of clinical response in LN
- CD163 is a biomarker present in cellular crescents, proliferative glomerular lesions, and acute tubulointerstitial lesions in patients with LN[7]
  - Urinary CD163 (uCD163) correlates with active LN inflammation and shows moderate concordance with UPCR and may represent a potential novel biomarker of activity[7]
- MISSION (NCT03393013) is designed to evaluate KZR-616 in patients with SLE with or without LN

Methods

- 2-part multicenter MISSION study of KZR-616 (**Figure 1**)
  - Part 1: Phase 1b, open-label dose-escalation study of KZR-616 in patients with SLE with or without nephritis
  - Part 2: Phase 2, open-label responder analysis of KZR-616 in patients with active proliferative LN (not reported here)
- Disease activity was assessed in the evaluable population, those intent-to-treat (ITT) participants who did not withdraw before week 13
- Safety and tolerability were assessed in the safety population, those receiving ≥1 dose of KZR-616

Figure 1. Study Design for the Phase 1b of MISSION



Abbreviation: QW, weekly.

- Doses up to 75 mg of KZR-616 were studied
- Tolerability measures were adjusted, and the formulation was changed from frozen to lyophilized for cohorts 2b/2c/3
- Pharmacokinetic and pharmacodynamic parameters were measured
- UPCR and uCD163 were measured in patients with active LN
- 24-hour uCD163 was measured by Meso Scale Diagnostics kits and normalized to creatinine

Results

- Part 1 is complete, with 47 participants receiving ≥1 dose of KZR-616, 95.7% of whom were women, with mean age of 50.6 years and mean disease duration of 9.2 years; 12 participants discontinued
  - Concomitant medications included prednisone (n=31, 66.0%, mean dosage: 8.6 mg/d), hydroxychloroquine (HCQ; n=24, 51.1%), methotrexate (n=9, 19.1%), azathioprine (n=6, 12.8%), and mycophenolate mofetil (n=6, 12.8%)

Table 1. Safety Data (Safety Population)

Measures	Cohort 1 (n=8)	Cohort 2 (n=5)	Cohort 2a (n=14)	Cohort 2b (n=6)	Cohort 2c (n=8)	Cohort 3 (n=6)	All patients (cohorts 1-3) (N=47)
Target dose, mg	45	60	60	60	60	75	45-75
Mean compliance, %	69.2	52.3	70.3	92.3	100	76.9	76.9
At least 1 TEAE	8 (100)	5 (100)	12 (85.7)	4 (66.7)	7 (87.5)	3 (50.0)	39 (83.0)
Most common TEAEs							
Injection-site erythema	5 (62.5)	2 (40.0)	5 (35.7)	2 (33.3)	6 (75.0)	0 (0)	20 (42.6)
Nausea	2 (25.0)	4 (80.0)	5 (35.7)	1 (16.7)	4 (50.0)	3 (50.0)	19 (40.4)
Vomiting	1 (12.5)	5 (100)	3 (21.4)	1 (16.7)	2 (25.0)	1 (16.7)	13 (27.7)
Infections and Infestations	1 (12.5)	0 (0)	5 (35.7)	2 (33.3)	2 (25.0)	1 (16.7)	11 (23.4)
Serious TEAEs	0 (0)	1 (20.0)	2 (14.3)	1 (16.7)	0 (0)	0 (0)	4 (8.5)
TEAEs leading to d/c of study drug	3 (37.5)	3 (60.0)	2 (14.3)	0 (0)	0 (0)	2 (33.3)	10 (21.3)
Patients receiving prednisone	5 (62.5)	5 (100)	10 (71.4)	4 (66.7)	5 (62.5)	3 (50.0)	31 (66.0)

Values are no. (%) unless otherwise specified. Cohorts 2b, 2c, and 3 (in blue) received a lyophilized formulation of KZR-616, prophylactic oral electrolyte solution, nonsedating antihistamines, antiemetics, and/or step-up dose. 2 additional discontinuations due to lost to follow-up and noncompliance were in cohort 2a. Data from April 5, 2021; pending final data cleaning.

Abbreviations: d/c, discontinuation; TEAE, treatment-emergent adverse event.

Table 2. Mean Disease Activity Scores Decreased Over Time With KZR-616 Treatment (Evaluable Population, n=35)

Instrument, mean (SD)	Baseline	Week 13 (end of treatment)	Week 25 (end of study)
SLEDAI-2K	9.1 (2.8)	6.6 (2.6)	7.1 (2.5)
CLASI-A	4.3 (4.1)	2.3 (3.0)	2.3 (3.2)
TJC	11.1 (6.3)	4.8 (4.7)	5.8 (5.1)
SJC	7.6 (5.6)	2.5 (3.7)	2.3 (2.7)
PhysGA	57.0 (21.7)	39.7 (23.5)	38.2 (17.6)
PtGA	58.3 (23.2)	38.2 (24.1)	42.7 (20.0)
HAQ-pain	58.5 (21.2)	43.1 (26.0)	41.7 (23.6)

Evaluable population are the ITT participants that did not withdraw before Week 13. Data from 5 April 2021; pending final data cleaning.

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.

Results (cont'd)

- Pharmacokinetics: SC bioavailability was ~100%; drug exposure increased dose proportionally with rapid absorption (T_{max}, 15-30 minutes) and clearance ($T_{1/2}$, ~2 hours)
- Pharmacodynamics: KZR-616 45 or 60 mg SC weekly selectively inhibits the immunoproteasome (data not shown)

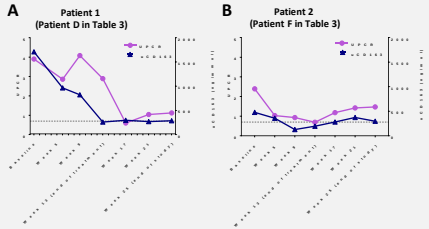
Table 3. Anti-dsDNA Antibody Titers Reduced Over Time for KZR-616 Treatment in Those With Elevated Levels at Baseline

Individual	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
Patient H[a]	162	−42.6	−33.3

[a]History of nephritis. [b]Active nephritis. Data from April 5, 2021; pending final data cleaning.

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

Figure 2. Improvements in UPCR and uCD163 Over Time With KZR-616 in 2 Patients With Lupus Nephritis



Dotted line indicates a 0.7 UPCR threshold. Urinary CD163 (uCD163) is normalized to urine creatinine. Patient 1 (cohort 2a, LN class IV/V) had a baseline stable treatment regimen of leflunomide, HCQ, and prednisone (10 mg/d) and had failed prior tacrolimus therapy. Patient 1 had drug holidays due to AEs, and therapy was reinitiated in this trial. Patient 1 was Patient D in Table 3. Patient 2 (cohort 2a; LN class III) had a baseline stable treatment regimen of mycophenolate mofetil (2 g), HCQ, and prednisone (10 mg/d). Patient 2 was Patient F in Table 3.

Abbreviations: AE, adverse event; anti-dsDNA, CD, cluster of differentiation; HCQ, hydroxychloroquine; LN, lupus nephritis; NA, not applicable; UPCR, urine protein to creatinine ratio.

Conclusions

- KZR-616 SC weekly for 13 weeks, up to 75 mg with step-up dosing, appears to be safe and well tolerated, and KZR-616 led to improvements on exploratory efficacy endpoints in patients with active SLE on stable background therapy in the phase 1b portion of MISSION
- The safety and tolerability with KZR-616 is favorable and is consistent with needs for a long-term therapy; safety concerns associated with immunosuppressive agents or dual proteasome inhibitors were not observed
- 2 of 2 patients with LN showed a >50% reduction from baseline in proteinuria and had favorable reductions in Systemic Lupus Erythematosus Disease Activity Index 2000 and anti–double-stranded DNA antibody (anti-dsDNA) levels with KZR-616
- uCD163, a marker for inflammatory activity in LN, also decreased from elevated levels over time in the 2 LN patients, demonstrating the anti-inflammatory effect of KZR-616
- Resolution seen in 5 of 10 patients with low C3 at baseline and in 4 of 6 patients with low C4 at baseline by Week 13 (data not shown)
- In all 8 patients with elevated anti-dsDNA levels at baseline (mean, 205.9 IU/mL), levels decreased by a mean of 41.9% at the end of treatment and by 45.1% at the end of the study
- Phase 2 studies are ongoing in LN (MISSION, 60 mg KZR-616, NCT03393013) and polymyositis and dermatomyositis (PRESIDIO, 45 mg KZR-616, NCT04033926); both studies have open-label extensions planned to collect long-term data

References

1. Basler M, et al. *Clin Exp Rheumatol.* 2015;(suppl 92);S74. 2. Muchamuel T, et al. *Ann Rheumatol Dis.* 2018;77(suppl 2);685. 3. Muchamuel T, et al. ASN 2020 Virtual Conference. 4. Kisselev AF, Groettrup M. *Curr Opin Chem Bio.* 2014;23(16-22). 5. Snyder B, et al. ACR/ARP 2019 Annual Meeting. 6. Fan RA, et al. ACR/ARP 2019 Annual Meeting. 7. Mejia-Vilet J, et al. *JASN.* 2020;31(6):1335-1347.

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