# Treatment of Systemic Lupus Erythematosus Patients with the Immunoproteasome Inhibitor KZR-616: Results from the First 2 Cohorts of an Open-label Phase 1b Dose Escalation Trial

FR0196

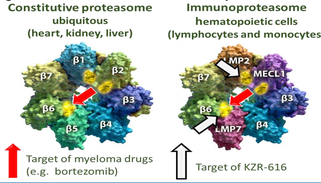
Richard Furie[1], Darrin Bomba[2], Maria Dall'Era[3], Massiel Prieto[4], Janet Anderl[2], Jinhai Wang[2], Christopher J. Kirk[2], Niti Goel[2, 5]

[1]Northwell Health, Great Neck, NY; [2]Kezar Life Sciences, South San Francisco, CA; [3]University of California San Francisco, San Francisco, CA; [4]Hope Clinical Trials, Miami, FL; [5]Duke University School of Medicine, Durham, NC; USA

## BACKGROUND

- Nonspecific proteasome inhibitors (eg, bortezomib [BTZ] and carfilzomib [CFZ]) target both forms of the proteasome (Figure 1) and are standard of care for multiple myeloma[1,2]
- BTZ has been used successfully to treat patients (pts) with systemic lupus erythematosus (SLE) and lupus nephritis (LN)[3-6]; however, adverse effects can prevent it from being utilized as a chronic treatment in autoimmune disorders
- KZR-616 (a CFZ analog), a first-in-class selective inhibitor of the immunoproteasome, is highly active in mouse models of SLE and LN[7]
- Subcutaneous (SC) KZR-616 at 30 and 45 mg weekly (QW) was safe and well tolerated, and achieved the target level of immunoproteasome inhibition in healthy volunteers (HV)[8]
- We report the preliminary safety and efficacy of KZR-616 in the open-label multicenter dose escalation Phase (Ph) 1b portion of the Ph 1b/2 MISSION (Modulator of the Immunoproteasome for Systemic Lupus with and without Nephritis) Study KZR-616-002 (NCT03393013)

**Figure 1. Proteasome subunit composition**




## OBJECTIVES

- Primary: Evaluate safety and tolerability of KZR-616
- Secondary: Evaluate KZR-616 pharmacokinetics (PK) and determine Ph 2 doses
- Exploratory: Evaluate the pharmacodynamics (PD) and efficacy of KZR-616

## METHODS

- All pts were enrolled in the United States
- Inclusion criteria:
  - SLE per Systemic Lupus International Collaborating Clinics Classification Criteria
  - SLE Disease Activity Index 2000 (SLEDAI) ≥4
  - Stable background immunosuppressant, antimalarial, and/or corticosteroid (≤20 mg prednisone equivalent) therapy
- KZR-616 administered at 45 mg (Cohort 1), 60 mg (Cohort 2), or with intrapt dose escalation from 30 to 60 mg (30-30-45-45-60 mg onwards) (Cohort 2a) SC QW through Week (W) 13 with follow-up through W25
- Safety assessments: Adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs), and laboratory tests
- PK and PD assessments at W1 (1st dose) and W5 (5th dose) as previously described[8]
- Efficacy assessments: SLEDAI, Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), 28 tender (T) and swollen (S) joint counts (JC), Physician Global Assessment (PhGA, 0-3 visual analog scale [VAS] converted to 100 mm for scoring), Patient Global Assessment (PtGA, 0-100 mm VAS), Patient Assessment of Pain due to illness (PtP, 0-100mm VAS) in evaluable pts
- Evaluable pts received ≥1 month of KZR-616; non-evaluable pts replaced
- No corrections for missing data implemented

## REFERENCES

1. Bross et al. Clin Cancer Res 2004.
2. Herndon et al. Clin Cancer Res 2013.
3. Alexander et al. ARD 2015.
4. de Groot et al. Lupus Sci Med 2015.
5. Zhang et al. Lupus 2017.
6. Sjowall C et al. Lupus 2017.
7. Muchamuel et al. ARD 2018. 77:A685.
8. Lickliter et al. ARD 2018. 77:A1413.
9. Yue et al. J Rheumatol 2018.
10. Yui et al. Am J Hematol 2016
11. Chakravarty et al. Lupus 2013.
12. Chanan-Khan et al. J Clin Oncol 2008.

## DEMOGRAPHICS

**Table 1. Baseline Demographics**

| Cohorts | Cohort 1 45 mg N=8 | Cohort 2 60 mg N=5 | Cohort 2a 30→60 mg N=11 | All KZR-616 N=24 |
|---|---|---|---|---|
| **Safety Population** | | | | |
| Age, years, mean (SD) | 51.9 (11.48) | 46.2 (11.32) | 56.8 (14.23) | 53.0 (12.96) |
| Female, n (%) | 8 (100) | 5 (100) | 9 (81.8) | 22 (91.7) |
| Race | | | | |
| White, n (%) | 7 (87.5) | 3 (60.0) | 10 (90.9) | 20 (83.3) |
| Black, n (%) | 1 (12.5) | 2 (40.0) | 1 (9.1) | 4 (16.7) |
| Hispanic ethnicity, n (%) | 4 (50.0) | 3 (60.0) | 9 (81.8) | 16 (66.7) |
| Body mass index, mean (SD) | 28.7 (6.82) | 27.4 (3.44) | 27.6 (3.16) | 27.9 (4.52) |
| SLE disease duration, months, mean (SD) | 107 (104.7) | 56 (58.1) | 80 (81.46) | 84 (84.7) |
| SLE medications, n (%) | 7 (87.5) | 5 (100.0) | 7 (63.6)** | 19 (79.2)** |
| Immunosuppressant(s), n (%) | 3 (37.5) | 3 (60.0) | 4 (36.4)** | 10 (41.7)** |
| Antimalarial, n (%) | 5 (62.5) | 5 (100.0) | 4 (36.4)** | 14 (58.4)** |
| Prednisone[6], n(%) | 5 (62.5) | 5 (100.0) | 6 (54.5)** | 16 (66.7)** |
| Prednisone dose, mean (SD)[6] | 8.8 (6.69) | 7.0 (2.74) | 7.5 (2.74)** | 7.8 (4.12)** |
| Completed Week 13*, n(%) | 5 (62.5) | 2 (40.0) | 4 (36.4)† | 11 (45.8)† |
| SLEDAI, mean (SD) | 9.4 (2.20) | 9.6 (2.61) | 9.5 (2.38) | 9.5 (2.27) |
| **Evaluable Population** | N=6 | N=3 | N=7† | N=16† |
| SLEDAI | | | | |
| Mean (SD) | 9.7 (1.97) | 10.0 (2.00) | 10.0 (2.31) | 9.9 (2.00) |
| Arthritis, n (%) | 6 (100.0) | 3 (100.0) | 7 (100.0) | 16 (100.0) |
| Mucocutaneous, n (%) | 6 (100.0) | 3 (100.0) | 7 (100.0) | 16 (100.0) |
| Proteinuria, n (%) | 0 (0) | 0 (0) | 1 (14.3) | 1 (6.3) |
| Low complement, n (%) | 2 (33.3) | 2 (66.7) | 4 (57.1) | 8 (50.0) |
| Increased DNA binding, n (%) | 0 (0) | 1 (33.3) | 1 (41.3) | 2 (12.5) |

[6]For pts on prednisone; ** Data not available for 4 pts; †Cohort 2a currently ongoing; *3 pts in Cohort 1 and 2 pts in Cohort 2 withdrew consent; 1 in Cohort 2 withdrew due to AE; in Cohort 2a, 1 pt lost to follow-up and 2 pts withdrew due to AEs

## SAFETY

**Table 2. Treatment Emergent Adverse Events (TEAEs)**

| n (%, # of AEs) | Cohort 1 45 mg N=8 | Cohort 2 60 mg N=5 | Cohort 2a 30→60 mg N=11 | All KZR-616 N=24 |
|---|---|---|---|---|
| TEAEs | 8 (100.0, 44) | 5 (100.0, 58) | 7 (63.6, 47) | 20 (83.3, 149) |
| TEAEs ≥Grade 3 | 0 (0, 0) | 1 (20.0, 1) | 1 (9.0, 1) | 2 (8.3, 2) |
| TEAEs leading to drug discontinuation | 0 (0, 0) | 1 (20.0, 1) | 2 (18.2, 2) | 3 (12.5, 3) |
| Serious TEAEs | 0 (0, 0) | 1 (20.0, 1) | 1 (9.0, 1) | 2 (8.3, 2) |
| Serious infectious TEAE | 0 (0, 0) | 0 (0, 0) | 1 (9.0, 1) | 1 (4.2, 1) |
| Non-serious infectious TEAE | 1 (12.5, 1) | 0 (0, 0) | 2 (18.2, 2) | 3 (12.5, 3) |
| Any injection site reaction (ISR) TEAE | 6 (75.0, 35) | 4 (80.0, 19) | 4 (36.4, 24) | 14 (58.3) |
| Any non-ISR TEAE in ≥2 pts | | | | |
| Nausea | 2 (25.0, 2) | 4 (80.0, 6) | 3 (27.3, 4) | 9 (37.5, 12) |
| Vomiting | 1 (12.5, 1) | 5 (100.0, 7) | 2 (18.2, 3) | 8 (33.3, 11) |
| Headache | 1 (12.5, 1) | 2 (40.0, 13) | 1 (9.1, 1) | 4 (16.7) |
| Dizziness | 1 (12.5, 1) | 2 (40.0, 2) | 0 (0, 0) | 3 (12.5) |
| Pyrexia | 0 (0, 0) | 2 (40.0, 2) | 1 (9.1, 4) | 3 (12.5) |
| Chills | 0 (0, 0) | 1 (20.0, 1) | 1 (9.1, 2) | 2 (8.3) |

- Majority of TEAEs mild and comprised injection site reactions (eg, erythema, induration, pain)
- Infectious TEAEs were 1 urinary tract infection, 1 upper respiratory tract infection, 1 oral candidiasis, and 1 herpes zoster
- 3 pts discontinued drug due to TEAEs: one in Cohort 2 and two in Cohort 2a, with 1 AE each of thrombotic microangiopathy (TMA), injection site erythema, and drug eruption
- No TEAEs of prolonged constitutional symptoms, peripheral neuropathy

## SAFETY

Vomiting TEAE

- Seen in 100% of Cohort 2
- Onset within 24 hours after initial dose of 60 mg; typically resolved within 24 hours of onset
- 2 pts discontinued, 3 pts deescalated to 45 mg
- 2 pts successfully achieved dosing with 60 mg without recurrent vomiting after 2-3 doses of 45 mg
- 2 pts successfully completed through W13: one on 60 mg QW, the other on 45 mg QW

Serious Adverse Events (n=2)

- Both events determined as related
- Cohort 2: Thrombotic microangiopathy (TMA), Grade 4 event, required hospitalization
  - 32 year old African American female with SLEDAI 12 at baseline (BL)
  - Hemoglobin decreased from 9.4 to 8.1 g/dL in the 4 weeks prior to BL
  - Antiphospholipid antibody status unknown (known association with TMA)
  - Had possible urinary tract infection
  - Event onset 5 days after first dose of KZR-616 at 60 mg
  - TMA known to be associated with SLE, infection
  - Drug-induced TMA rare AE associated with nonselective proteasome inhibitors[9, 10]
- Cohort 2a: Shingles (localized herpes zoster), Grade 3 medically important event (not requiring hospitalization)
  - 32 year old Hispanic male on azathioprine, prednisone, and ibuprofen
  - SLEDAI 12 at BL; no history of chickenpox; no prior shingles vaccination
  - Event onset occurred after 3rd dose (45 mg) of KZR-616
  - Responded to valacyclovir; resumed and completed dosing with KZR-616
  - Increased risk of zoster associated with SLE; azathioprine and prednisone use
  - Herpes zoster is an AE reported with nonselective proteasome inhibitors[11, 12]

Other

- Only 1 isolated laboratory value ≥Grade 3 reported in pt with normal value at BL: Grade 3 neutropenia in Cohort 1 pt occurred at W4; pt completed study without recurrence
- Other laboratories, vital signs, ECGs without significant changes from BL

## PHARMACOKINETICS and PHARMACODYNAMICS

PK (Table 3) and PD (Table 4) in SLE pts were similar to that achieved for the same doses in HV

**Table 3. Pharmacokinetics: Mean (SD) Maximum and Total Exposure**

| Dose (mg) | Population | Dose day | N | $C_{max}$ (ng/mL) | $AUC_{last}$ (h*ng/mL) |
|---|---|---|---|---|---|
| 45 | HV[8] | 1 | 6 | 102 (26.7) | 354 (38.7) |
| | | 22 | 18 | 141 (57.7) | 376 (67.6) |
| | SLE | 1 | 8 | 100 (46.9) | 249 (115) |
| | | 29 | 7 | 145 (93.1) | 372 (163) |
| 60 | HV[8] | 1 | 12 | 160 (61.1) | 411 (85.8) |
| | SLE | 1 | 5 | 158 (58.4) | 386 (237) |

$C_{max}$=maximum concentration; AUC=area under the concentration time curve.

**Table 4. Mean (SEM) Proteasome Activity Inhibition and Active Site Subunit Occupancy**

| | | | Constitutive proteasome | | Immunoproteasome | | |
|---|---|---|---|---|---|---|---|
| Dose (mg) | Population | N | Whole blood enzymatic activity inhibition | β5 occupancy | PBMC enzymatic activity inhibition | LMP7 occupancy | LMP2 occupancy |
| 45 | HV[8] | 6 | 31.9 (4.6) | 25.9 (6.0) | 90.2 (0.7) | 94.3 (0.4) | 71.0 (2.8) |
| | SLE | 7 | 34.1 (8.2) | 27.4 (7.0) | 74.6 (12.6) | 80.2 (13.4) | 55.6 (10.5) |
| 60 | HV[8] | 12 | 50.8 (2.9) | 36.9 (3.5) | 91.8 (0.51) | 95.2 (0.95) | 62.0 (2.5) |
| | SLE | 5 | 31.3 (15.7) | 34.7 (11.7) | 76.4 (12.6) | 75.4 (18.9) | 57.9 (14.7) |

## EFFICACY

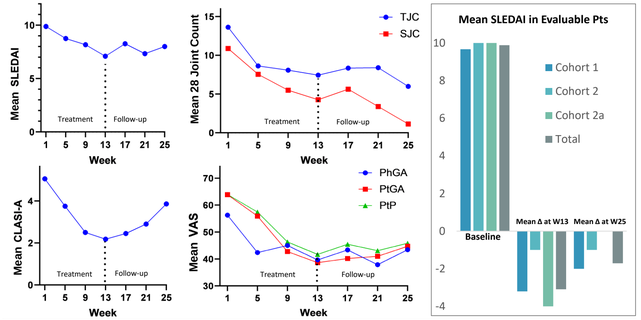



**Table 5. Evaluable Patient Data From Baseline Through Week 13**

| Patient (Cohort) | Dose (mg) | SLEDAI | | 28 TJC | | 28 SJC | | CLASI-A | | PhGA | | PtGA | | PtP | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | BL | W13 | BL | W13 | BL | W13 | BL | W13 | BL | W13 | BL | W13 | BL | W13 |
| 103-001 (1) | 45 | 10 | 10 | 22 | 12 | 22 | 12 | 7 | 3 | 78 | 41 | 93 | 80 | 98 | 88 |
| 104-001 (1) | 45 | 10 | 6 | 12 | 14 | 10 | 10 | 4 | 3 | 78 | 77 | 79 | 76 | 60 | 78 |
| 107-001 (1) | 45 | 10 | 4 | 10 | 0 | 4 | 0 | 3 | 2 | 43 | 9 | 28 | 16 | 46 | 20 |
| 107-004 (1)* | 45 | 10 | NA | 4 | NA | 8 | NA | 4 | NA | 69 | NA | 64 | NA | 70 | NA |
| 111-002 (1) | 45 | 12 | 6 | 26 | 0 | 10 | 0 | 8 | 3 | 49 | 42 | 48 | 26 | 63 | 28 |
| 116-005 (1) | 45 | 6 | 6 | 12 | 12 | 12 | 0 | 1 | 1 | 33 | 30 | 33 | 20 | 50 | 30 |
| 103-005 (2)* | 60 | 10 | NA | 14 | NA | 12 | NA | 8 | NA | 75 | NA | 79 | NA | 79 | NA |
| 104-007 (2) | 45 | 12 | 10 | 15 | 11 | 10 | 7 | 8 | 3 | 82 | 45 | 81 | 40 | 83 | 42 |
| 116-007 (2) | 60 | 8 | 8 | 6 | 6 | 6 | 0 | 3 | 3 | 33 | 30 | 60 | 30 | 50 | 30 |
| 102-004 (2a) | 60 | 12 | 4 | 21 | 0 | 14 | 1 | 4 | 2 | 44 | 3 | 77 | 1 | 78 | 2 |
| 102-006 (2a)* | 60 | 8 | NA | 10 | NA | 10 | NA | 5 | NA | 53 | NA | 85 | NA | 83 | NA |
| 104-008 (2a) | 60 | 14 | 12 | 8 | 9 | 7 | 7 | 4 | 2 | 85 | 71 | 90 | 62 | 83 | 67 |
| 112-009 (2a)** | 60 | 8 | NA | 11 | NA | 4 | NA | 2 | NA | 43 | NA | 47 | NA | 26 | NA |
| 116-009 (2a) | 60 | 8 | 6 | 18 | 10 | 18 | 10 | 2 | 1 | 33 | 28 | 45 | 34 | 45 | 34 |
| 116-010 (2a) | 60 | 10 | 6 | 22 | 8 | 22 | 0 | 5 | 1 | 66 | 55 | 60 | 40 | 60 | 40 |
| 121-004 (2a)** | 60 | 10 | NA | 7 | NA | 5 | NA | 13 | NA | 36 | NA | 53 | NA | 49 | NA |

*Pt discontinued before W13; **Pt ongoing.

For evaluable pts reaching W13 (n=11)

- SLEDAI: 8 pts with decrease ≥2 points; 5 pts with decrease ≥4 points
- SJC/TJC: 4 (TJC) and 6 (SJC) pts had ≥50% improvement
- CLASI-A: 4 of 7 pts with CLASI-A ≥4 at BL had decrease ≥4 points
- PhGA/PtGA/PtP: 6, 10, and 10 pts had ≥10-point reduction, respectively
- Complement: 3 of 6 pts with low levels at BL had resolution

## CONCLUSIONS

- **Repeat dosing of KZR-616 was well tolerated at 45 mg as well as at 60 mg following intrapatient dose escalation**
- **No prolonged hematologic or constitutional AEs (including peripheral neuropathy) as seen with nonselective proteasome inhibitors**
- **Consistent PK and PD in SLE patients compared to healthy volunteers**
- **Evidence of efficacy across all measures assessed at Week 13 with maintenance of benefit through 12 weeks post last dose except rash (CLASI-A subdomain)**
- **Initial doses planned for the Phase 2 clinical program in lupus nephritis, dermatomyositis and polymyositis, and autoimmune hemolytic anemia and immune thrombocytopenia will be 30 and 45 mg**

We thank all the investigators, site staff, and especially the patients who have contributed their time and efforts to this study.