



Lupus nephritis-clinical: LO-017

# **Zetomipzomib (KZR-616) demonstrates anti-inflammatory and immunomodulatory potential in patients with active lupus with or without lupus nephritis: Results from the open-label Phase 1b/2 MISSION study**

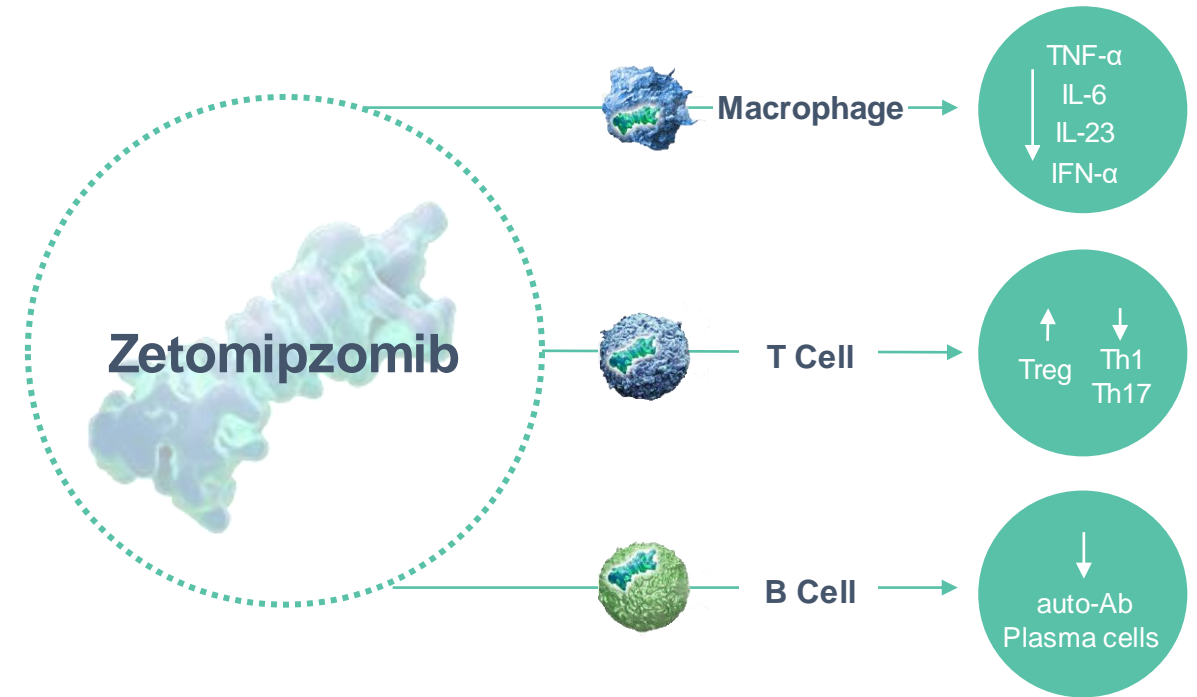
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# Zetomipzomib (KZR-616): A First-in-Class, Small Molecule Selective Immunoproteasome Inhibitor

## What is immunoproteasome?

- Immunoproteasomes are abundantly expressed in immune effector cells (e.g., T cells, B cells)
- Increased expression of the immunoproteasome is observed at sites of inflammation (e.g., kidneys of patients with LN)
- Immunoproteasomes act as a master regulator of multiple cellular functions
- When immunoproteasomes are inhibited, multiple pathways involved in inflammatory cytokine production and immune effector cell activity are also inhibited
- Immunoproteasomes are involved in the pathogenesis of many autoimmune diseases

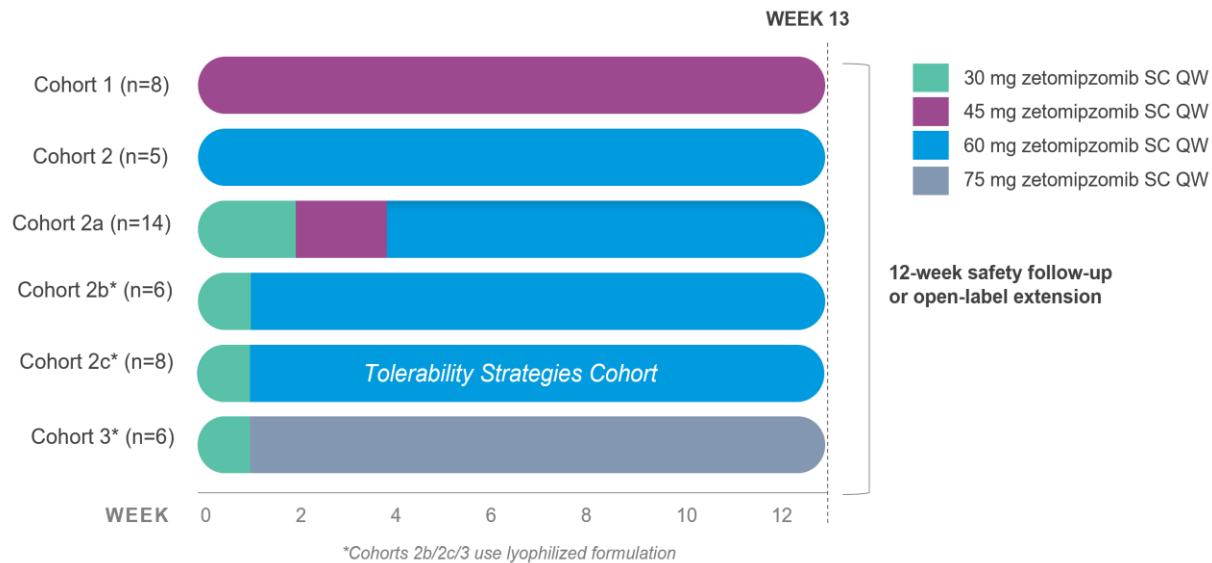


***A therapeutic that selectively inhibits the immunoproteasome has broad potential across a range of conditions including systemic lupus erythematosus and lupus nephritis***

# MISSION Phase 1b: Study Design and Baseline Characteristics

- Open-label dose-escalation study to evaluate the safety and tolerability of zetomipzomib in patients with SLE ± LN

## Phase 1b: Study Schema



### Endpoints:

- Primary:** Safety and tolerability
- Secondary:** Recommended Phase 2 dose and pharmacokinetics
- Exploratory:** Efficacy, pharmacodynamics and biomarkers

	Zetomipzomib (N=47)
<b>Age, year, mean (SD)</b>	50.6 (13.5)
<b>Sex, n (%)</b>	
Female	45 (95.7)
<b>Race, n (%)</b>	
White	36 (76.6)
Black or African American	10 (21.3)
Asian	1 (2.1)
<b>Ethnicity, n (%)</b>	
Hispanic/Latino	27 (57.4)
<b>SLE duration, years, mean (SD)</b>	9.2 (11.7)
<b>Concomitant medications, n (%)</b>	
Corticosteroids	32 (68.1)
Hydroxychloroquine	35 (74.5)
Methotrexate	9 (19.1)
Azathioprine	6 (12.8)
Mycophenolate mofetil	6 (12.8)
<b>Prednisone (or equivalent) dose, mg, mean (SD)</b>	9.1 (4.5)

47 patients received ≥1 dose of zetomipzomib (safety population) and 12 patients discontinued before end of treatment (evaluable population, n=35).

**Abbreviations:** EOT, end of treatment; EOS, end of study; LN, lupus nephritis; QW, once every week; SC, subcutaneous; SFU, safety follow-up; SLE, systemic lupus erythematosus; UPCR, urine protein to creatinine ratio.

**References:** 1. <https://clinicaltrials.gov/ct2/show/NCT03393013>. 2. Furie et al. 2021 EULAR Virtual Congress. 3. Data on file.

# MISSION Phase 1b: SLE Disease Activity Scores and Safety

## SLE Disease Activity Scores

Instrument, mean (SD)	MISSION Phase 1b n=35		
	Baseline	Week 13 (EOT)	Week 25 (EOS)
SLEDAI-2K	9.1 (2.8)	6.6 (2.6)	7.1 (2.6)
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)
PhyGA	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)

## Summary of Adverse Events

Adverse Events, n (%)	MISSION Phase 1b Zetomipzomib N=47
Most common TEAE: Injection-site reaction	28 (59.6)
TEAE leading to study drug discontinuation	10 (21.3)*
Serious TEAE	4 (8.5) <sup>^</sup>
Grade ≥3 TEAE	5 (10.6) <sup>†</sup>
Opportunistic Infections	0 (0)
Death	0

\*9 related TEAEs (nausea [n=2], vomiting, injection site induration, injection site pain, injection site pruritus, lipohypertrophy, erythematous rash, generalized skin rash) and 1 related serious TEAE (thrombotic microangiopathy [TMA]) led to study drug discontinuation. <sup>^</sup>3 related serious TEAEs (Grade 2 viral infection from cohort 2b, Grade 3 herpes zoster from cohort 2a, Grade 3 systemic inflammatory response syndrome[SIRS] from cohort 2a) were reported. Study drug was temporarily interrupted, and patients have recovered and completed the study. <sup>†</sup>1 Grade 4 TEAE of TMA was reported in Phase 1b, and no Grade 4 TEAE was reported in Phase 2.

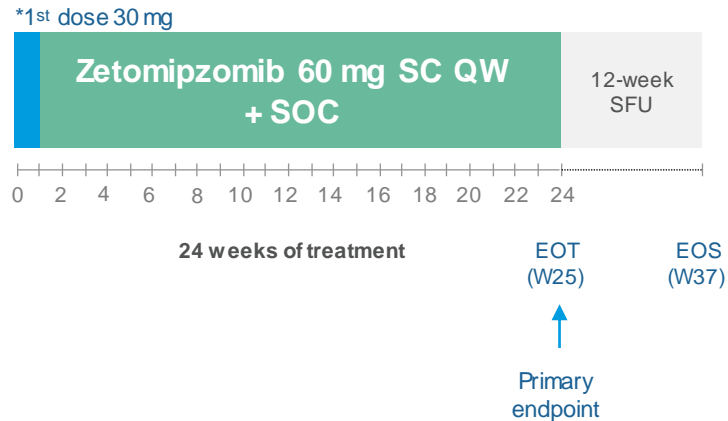
Evaluable population (n=35) are patients that did not withdraw before end of treatment. Safety population (N=47) are patients who received ≥1 dose of zetomipzomib.

**Abbreviations:** CLASI-A, Cutaneous Lupus Erythematosus Severity Index-Activity; EOS, end of study; EOT, end of treatment; PhyGA, Physician Global Assessment; PtGA, Patient Global Assessment; SD, standard deviation; SJC, swelling joint count; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; TJC, tender joint count.

**References:** 1. Furie et al. 2021 EULAR Virtual Congress. 2. Data on file.

# MISSION Phase 2: Study Design and Baseline Characteristics

- Open-label study to evaluate the efficacy and safety of zetomipzomib in patients with active proliferative LN (Class III or IV ± Class V) with 24-hour urine protein to creatinine ratios (UPCR) ≥1.0 mg/mg despite stable background therapy



	Zetomipzomib N=21
<b>Age (years), mean (SD)</b>	35.3 (11.6)
<b>Female, n (%)</b>	19 (90.5)
<b>Race, n (%)</b>	
White	7 (33.3)
Black or African American	1 (4.8)
Asian	1 (4.8)
Other	12 (57.1)
<b>Ethnicity, n (%)</b>	
Hispanic or Latino	11 (52.4)
<b>SLE duration (years), mean (SD)*</b>	9.7 (7.2)
<b>LN duration (years), mean (SD)</b>	5.3 (4.8)
<b>LN class type, n (%)</b>	
Class III only	6 (28.6)
Class IV only	11 (52.4)
Class III + V	3 (14.3)
Class IV + V	1 (4.8)

	Zetomipzomib N=21
<b>Most recent kidney biopsy, n (%)</b>	
Within 6 months	13 (61.9)
Within 6-12 months	5 (23.8)
Within 12-24 months	3 (14.3)
<b>24-hour UPCR (mg/mg), mean (SD)</b>	2.6 (2.6)
<b>eGFR (mL/min/1.73 m<sup>2</sup>), mean (SD)</b>	104.7 (32.6)
<b>Prednisone (or equivalent) dose (mg/d), mean (SD)</b>	18.8 (12.4)
<b>Concomitant medications, n (%)</b>	
Prednisone (or equivalent)	21 (100)
Mycophenolate mofetil or mycophenolic acid	20 (95.2)
Hydroxychloroquine	14 (66.7)
Azathioprine	2 (9.5)

## Endpoints:

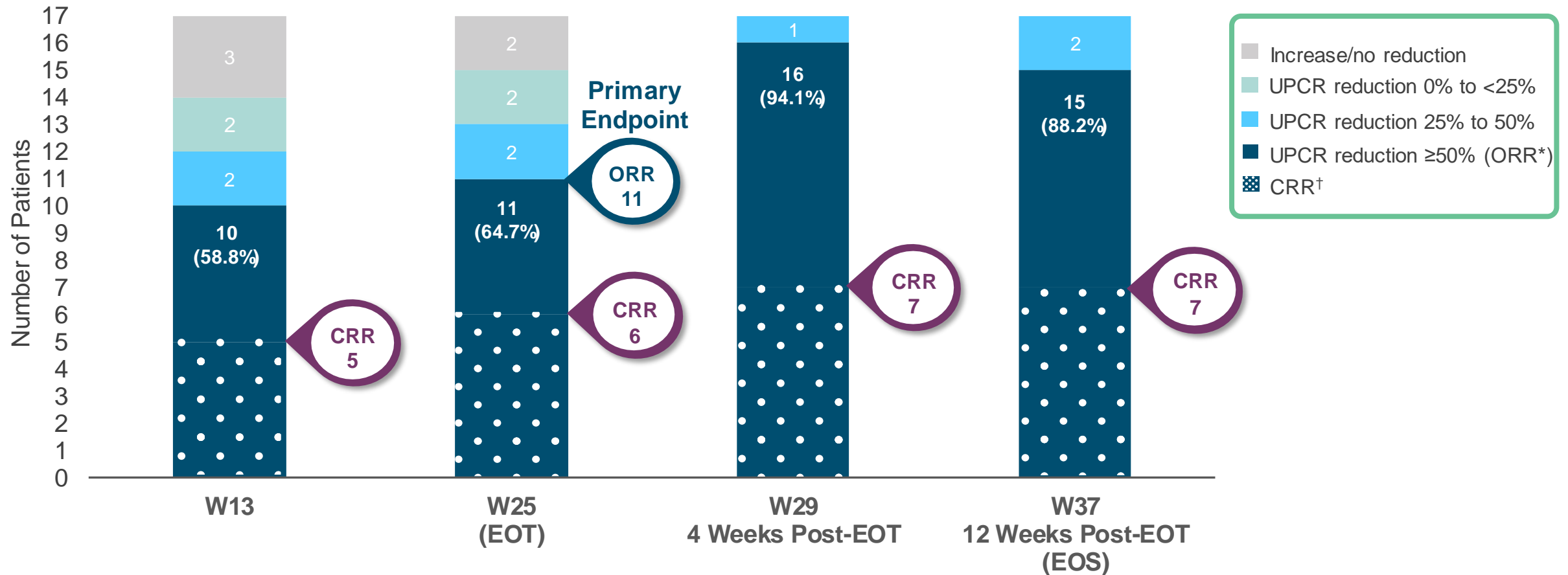
- Primary:** Proportion of patients with ≥50% reduction in UPCR
- Secondary:** Safety/tolerability, additional renal response parameters (e.g., Complete Renal Response)
- Exploratory:** SLE clinical disease activity measures and biomarkers

21 patients received ≥1 dose of zetomipzomib (safety population in protocol amendment 4) and 4 patients discontinued before end of treatment (evaluable population, n=17).

**Abbreviations:** EOT, end of treatment; EOS, end of study; LN, lupus nephritis; QW, once every week; SC, subcutaneous; SFU, safety follow-up; SLE, systemic lupus erythematosus; SOC, standard of care; UPCR, urine protein to creatinine ratio.

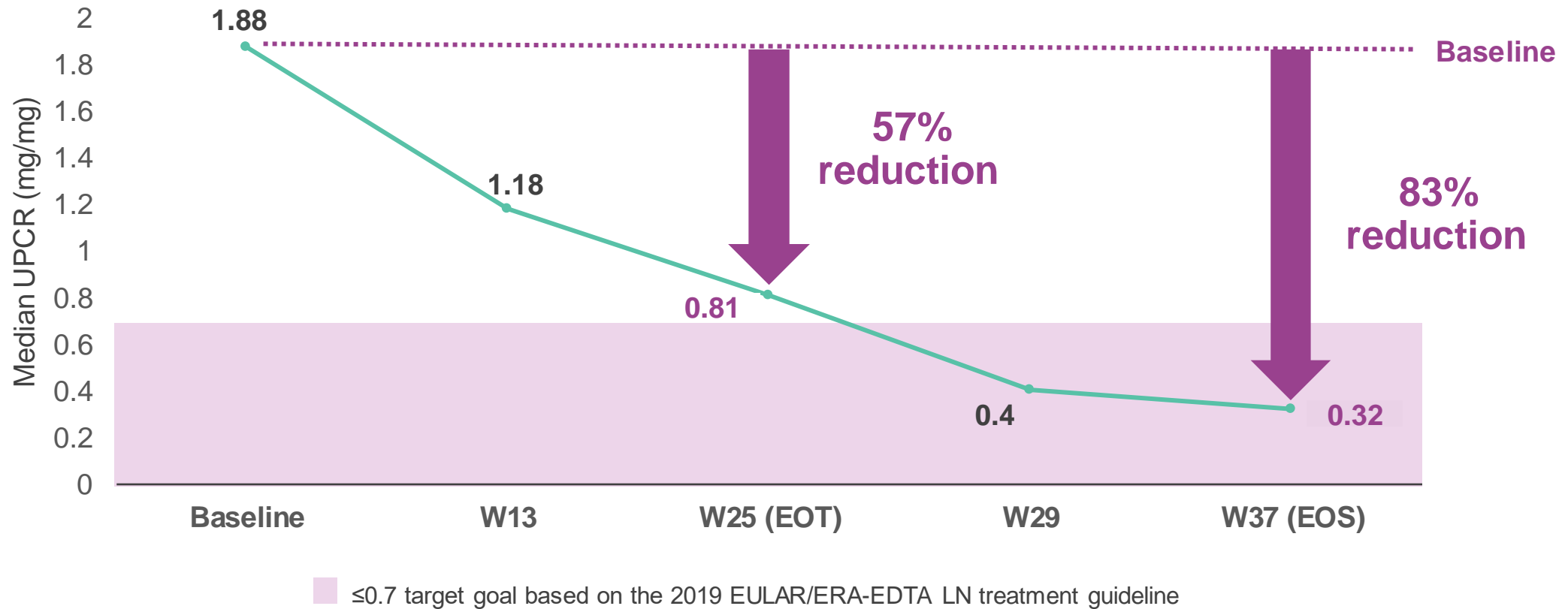
**References:** 1. <https://clinicaltrials.gov/ct2/show/NCT03393013>. 2. Furie et al. 2021 EULAR Virtual Congress. 3. Parikh SV, et al. 2022 ASN Kidney Week.

# MISSION Phase 2: Zetomipzomib Treatment Demonstrated Clinically Meaningful Renal Responses (Evaluable Population, n=17)



\*ORR: ≥50% reduction in UPCR compared to baseline †CRR: UPCR ≤0.5, eGFR ≥60 mL/min/1.73m<sup>2</sup> or no worsening of eGFR from baseline of ≥25%, prednisone (or equivalent) ≤10 mg and no use of prohibited medication

# MISSION Phase 2: Median UPCR Was Reduced to 0.32 mg/mg by the End of Study (Evaluable Population, n=17)



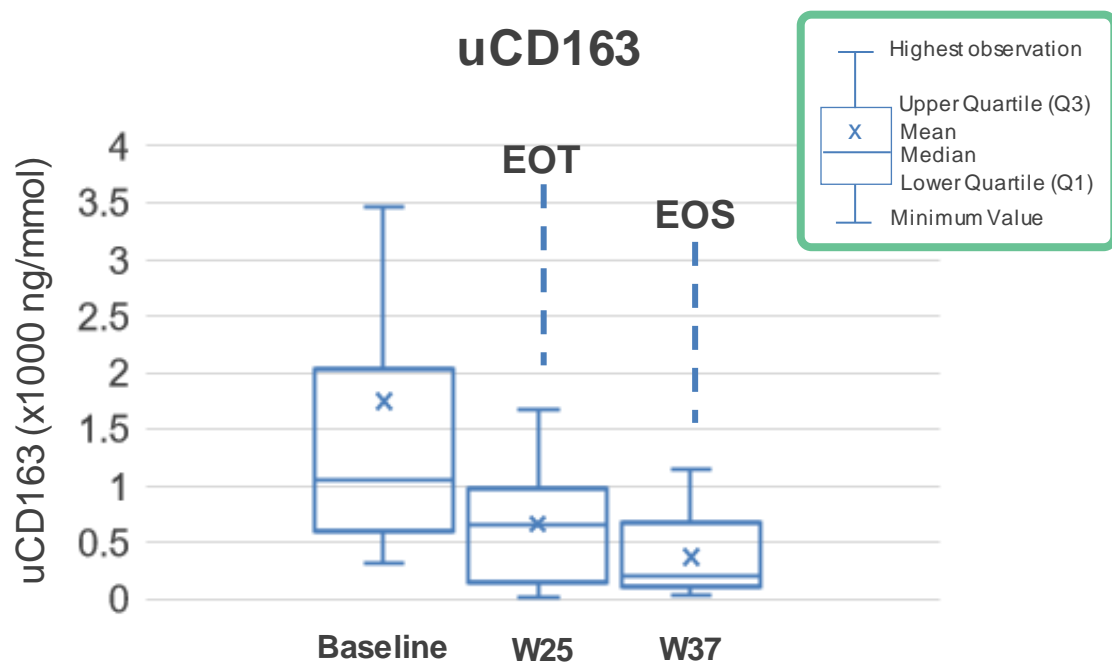
Evaluable population (n=17) are patients that did not withdraw before Week 25; Patients received 24 weeks of zetomipzomib; End-of-treatment assessments performed at Week 25.  
Reference: Parikh SV, et al. 2022 ASN Kidney Week. Abbreviations: EOT, end of treatment; EOS, end of study; W, week.

## MISSION Phase 2: Other Efficacy Data

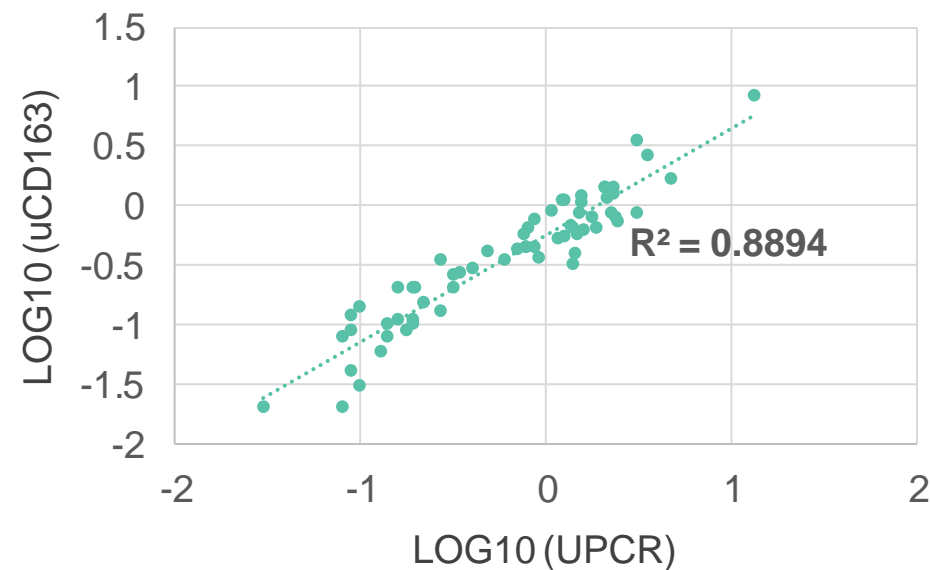
- **Stable eGFR** over 9 months of observation
- By Week 13, **82.4%** (14/17) of patients achieved a daily glucocorticoid dose of  $\leq 10$  mg and a **58%** reduction in mean daily dose by Week 25 (EOT)
- By Week 25 (EOT)
  - **42%** (5/12) of patients with a high anti-dsDNA titer normalized
  - **40%** (2/5) of patients with a low C3 level normalized
  - **50%** (2/4) of patients with a low C4 level normalized



# MISSION Phase 2: Zetomipzomib Decreased Urinary CD163\*, an Inflammatory Marker Shown to Correlate With UPCR (n=13<sup>†</sup>)



## Correlation Between UPCR and uCD163



\*CD163 is a transmembrane protein mainly expressed by M2c macrophages that infiltrate tissues during the “healing phase” of inflammation. uCD163 was normalized to the urine creatinine for analysis. <sup>†</sup>13/17 evaluable patients consented to urine biomarker analysis.

## MISSION Phase 2: Safety and Tolerability

Adverse Events, n (%)	MISSION Phase 2 Zetomipzomib N=21
Most common TEAE: Injection-site reaction	15 (71.4)
TEAE leading to study drug discontinuation	4 (19.0) <sup>†</sup>
Serious TEAE	2 (9.5) <sup>‡</sup>
Grade ≥3 TEAE	6 (28.6) <sup>*</sup>
Opportunistic Infections	0 (0)
Death	0 (0)

<sup>†</sup>3 related TEAEs (injection site infiltration, asthenia, reticulocyte increase) and 1 unrelated serious TEAE (worsening pulmonary arterial hypertension [PAH] with acute kidney injury [AKI] and urinary tract infection [UTI]) led to study drug discontinuation. Patient subsequently had SAEs of AKI and UTI (unrelated) and has recovered. <sup>\*</sup>1 related serious TEAE of acute protracted migraine was reported. Study drug was temporarily interrupted, and patient has recovered and completed the study. <sup>\*</sup>1 Grade 4 TEAE of TMA was reported in Phase 1b, and no Grade 4 TEAE was reported in Phase 2.

# Conclusions



In the MISSION open-label study, zetomipzomib treatment demonstrated clinically meaningful renal responses in LN patients who had not responded to SOC therapy



Zetomipzomib once-weekly demonstrated a favorable safety and tolerability profile with no evidence of immunosuppression (no clinically significant opportunistic infections or immune cell depletion and no serious infections) to date



Zetomipzomib is being further evaluated in patients with active LN in a larger placebo-controlled Phase 2b trial (PALIZADE; NCT05781750; KZR-616-202)