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KIDNEY WEEK 2025

Safety and Preliminary Efficacy of Zetomipzomib from the PALIZADE Phase 2b Clinical Trial in Patients with Lupus Nephritis

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Disclosures

- Consultant and Investigator for Kezar Life Sciences

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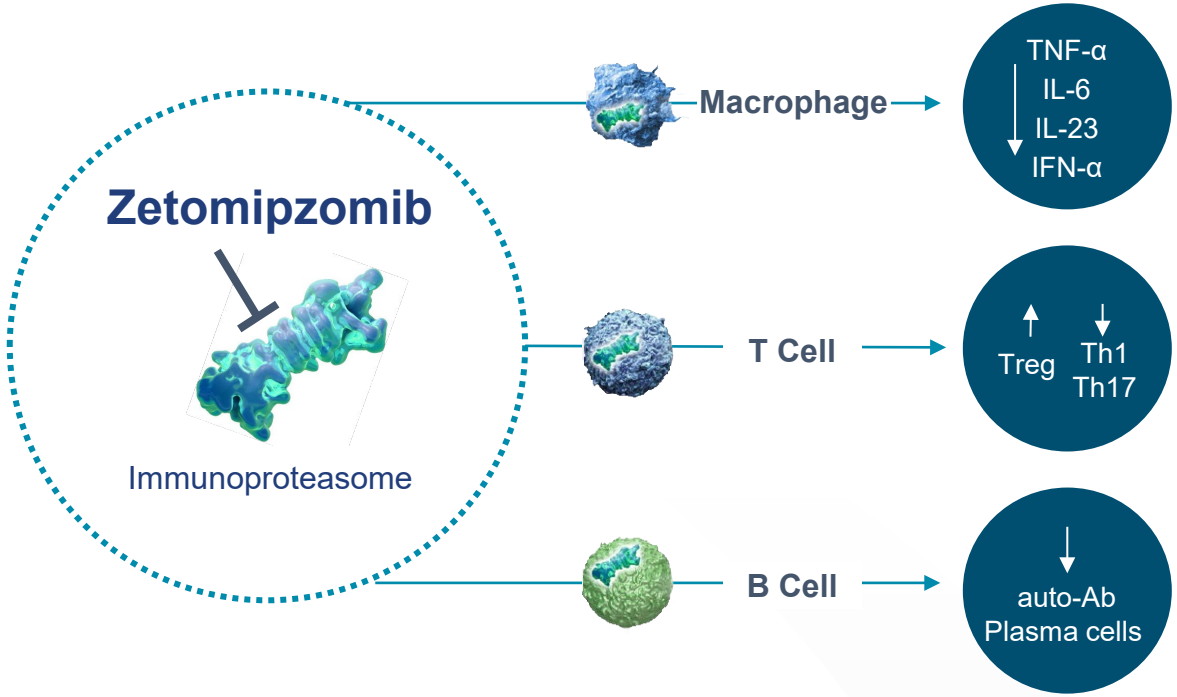
Zetomipzomib (KZR-616): A First-in-Class, Small Molecule Selective Immunoproteasome Inhibitor

What is an 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 lupus nephritis).
- Immunoproteasome inhibition results in downregulation of multiple cytokines and immune effector pathways involved in disease pathogenesis.
- Immunoproteasome inhibitors are active in multiple models of autoimmune diseases.



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

References: 1. Muchamuel T, et al. *Front Immunol*. 2023;14:1043680. 2. Kirk et al. *Cells*. 2021;11(1):9.

Key Attributes of Zetomipzomib, a First-in-Class Selective Immunoproteasome Inhibitor

Preclinical

- Zetomipzomib ameliorates nephritis progression in murine models of lupus.[1]
- Normal immune mechanisms to viral challenge and vaccination remain intact.[1]
- No teratogenicity observed in animal models[2]

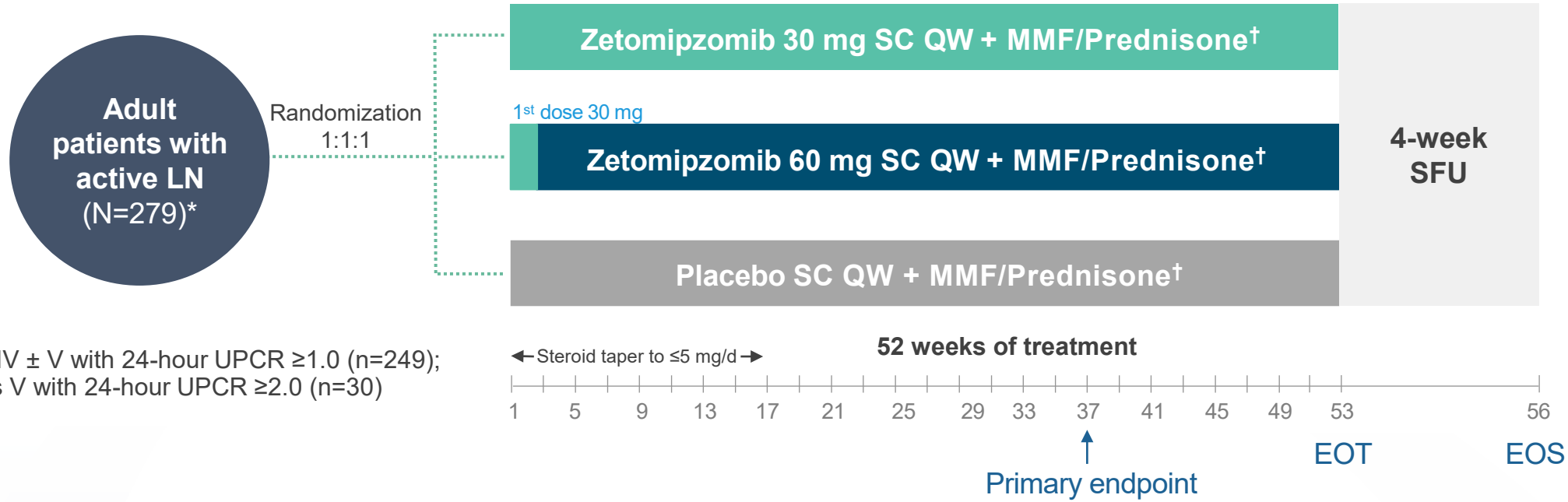
Clinical

- MISSION open-label study (NCT03393013) → zetomipzomib treatment demonstrated clinically meaningful renal responses without pulse IV steroid induction therapy in LN patients who had not responded to SOC therapy.[3]
- Once-weekly SC injection leads to intermittent inhibition of the immunoproteasome[3]
  - Rapid absorption and clearance ($T_{1/2}$ <5 hours) following SC administration
  - No accumulation observed with repeat dosing
- No predicted clinically significant drug-drug interactions[4,5]
- No serum monitoring required[4]

Renal Response, n (%)	MISSION Phase 2 Zetomipzomib 60 mg N=17*
ORR†	
Week 25 (EOT)	11 (64.7)
Week 37 (EOS)	15 (88.2)
CRR‡	
Week 25 (EOT)	6 (35.3)
Week 37 (EOS)	7 (41.2)

*Evaluable population (n=17) are patients that did not withdraw before week 25 in amendment 4 of the open-label MISSION phase 2 study; patients received 24 weeks of zetomipzomib; end-of-treatment assessments performed at week 25.
†ORR: ≥50% reduction in UPCR compared to baseline.
‡CRR: UPCR ≤0.5, eGFR ≥60 mL/min/1.73m2 or no worsening of eGFR from baseline of ≥25%, prednisone (or equivalent) ≤10 mg and no use of prohibited medication.
Abbreviations: CRR, complete renal response; IV, intravenous; LN, lupus nephritis; ORR, overall renal response; SC, subcutaneous; SOC, standard of care; $T_{1/2}$, half-life.
References: 1. Muchamuel T, et al. *Front Immunol*. 2023;14:1043680. 2. Kezar Life Sciences. Data on file. 3. Parikh SV, et al. 2022 ASN Kidney Week. 4. Lickliter J, et al. Poster presented at: ACR 2017; San Diego, California, USA; November 3-8, 2017. 5. Fang et al. *Drug Metab Dispos*. 2021;49(9):810-821.

PALIZADE: Phase 2b Placebo-Controlled Trial Evaluating the Efficacy and Safety of Zetomipzomib in Participants with Active LN



Notable differences from MISSION Phase 2a (as requested by FDA):

- Pulse IV steroid treatment
- Inclusion of isolated Class V LN

Primary Endpoint: Proportion of participants achieving CRR (UPCR ≤0.5 and eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease of >20% from baseline eGFR) at week 37.
†MMF or equivalent (1-3 g/d; target dose 2 g/d), oral corticosteroids (0.3-0.5 mg/kg/d [maximum 40 mg/d], which were tapered to 5 mg/d after 16 weeks) and IV methylprednisolone on Day 1 (500 mg-1g weight-based dosing, up to 3 gm).
Abbreviations: EOS, end of study; EOT, end of treatment; IV, intravenous; MMF, mycophenolate mofetil; PBO, placebo; QW, once weekly; SC, subcutaneous; SFU, safety follow-up; UPCR, urine protein to creatinine ratio.
References: 1. Clinicaltrials.gov Accessed April 11, 2023. https://clinicaltrials.gov/ct2/show/NCT05781750. 2. Kezar Life Sciences. Data on file.

Key Demographic and Baseline Characteristics (Safety Population)

	Zetomipzomib 30 mg N=27	Zetomipzomib 60 mg N=29	Placebo N=28	All participants N=84
Age, mean (SD), years	31.0 (10.5)	32.5 (9.4)	32.8 (9.1)	32.1 (9.6)
Female, n (%)	25 (92.6)	28 (96.6)	25 (89.3)	78 (92.9)
Race, n (%)				
White	6 (22.2)	7 (24.1)	9 (32.1)	22 (26.2)
Black or African American	1 (3.7)	1 (3.4)	3 (10.7)	5 (6.0)
Asian	19 (70.4)	15 (51.7)	13 (46.4)	47 (56.0)
American Indian or Alaskan Native	1 (3.7)	5 (17.2)	2 (7.1)	8 (9.5)
Other	0 (0.0)	1 (3.4)	1 (3.6)	2 (2.4)
Ethnicity, n (%)				
Hispanic or Latino	5 (18.5)	10 (34.5)	13 (46.4)	28 (33.3)
SLE duration, mean (SD), years	4.7 (5.0)	8.1 (6.2)	6.7 (5.8)	6.5 (5.8)
LN duration, mean (SD), years	1.8 (2.3)	5.0 (5.4)	4.3 (4.5)	3.7 (4.5)
LN class, n (%)				
Class III only	4 (14.8)	8 (27.6)	5 (17.9)	17 (20.2)
Class IV only	10 (37.0)	13 (44.8)	12 (42.9)	35 (41.7)
Class III + V	5 (18.5)	3 (10.3)	3 (10.7)	11 (13.1)
Class IV + V	4 (14.8)	2 (6.9)	5 (17.9)	11 (13.1)
Pure Class V	4 (14.8)	3 (10.3)	3 (10.7)	10 (11.9)

Abbreviations: LN, lupus nephritis; SD, standard deviation; SLE, systemic lupus erythematosus.

Key Demographic and Baseline Characteristics (Safety Population) – Cont'd

	Zetomipzomib 30 mg N=27	Zetomipzomib 60 mg N=29	Placebo N=28	All participants N=84
24-hour UPCR, mean (SD), mg/mg	3.7 (2.0)	3.6 (2.1)	3.1 (1.6)	3.5 (1.9)
SLEDAI-2K, mean (SD)	11.8 (5.3)	11.7 (5.5)	10.5 (5.0)	11.3 (5.2)
eGFR, mean (SD), mL/min/1.73 m^2	113.0 (27.6)	97.6 (32.5)	114.0 (26.8)	108.0 (29.8)
Concomitant medications, n (%)				
MMF (or equivalent)	27 (100.0)	29 (100.0)	28 (100.0)	84 (100.0)
Prednisone (or equivalent)	27 (100.0)	28 (96.6)	28 (100.0)	83 (98.8)
IV Methylprednisolone	22 (81.5)	23 (79.3)	23 (82.1)	68 (81.0)
Antimalarial (e.g. hydroxychloroquine)	25 (92.6)	24 (82.8)	25 (89.3)	74 (88.1)

Abbreviations: eGFR, estimated glomerular filtration rate; IV, intravenous; MMF, mycophenolate mofetil; SD, standard deviation; SLEDAI-2K, Systemic Lupus Erythematosus Activity Index 2000; UPCR, urine protein to creatinine ratio.

PALIZADE Enrollment Metrics and Trial Termination

- Trial halted following 4 fatalities occurring in Argentina and the Philippines (1 - PBO, 2 - 30 mg arm, 1 - 60 mg arm*) and other treatment-emergent serious adverse events (TESAEs) with similar patterns and proximity to dosing (i.e. Systemic Injection Reactions).
- 84 patients enrolled at the time of termination (October 2024) with 56% of patients enrolled in APAC region
  - All enrolled participants were included in the safety analysis.
  - Prior to termination, the discontinuation rate was less than 15%.
- Independent Data Monitoring Committee (IDMC) recommended suspending enrollment and dosing following 15 SAEs (18% of enrolled patients), including 4 fatalities (4.7%).
- Among 11 patients with non-fatal Serious Adverse Events (SAEs):
  - 4 patients experienced Grade 1 and 2 events (1 placebo, 3 in 60 mg arm).
  - 4 patients experienced Grade 3 events (2 in 30 mg arm, 2 in 60 mg arm) deemed related by the principal investigator.
  - 3 patients experienced Grade 3 events (1 in 30 mg arm, 2 in 60 mg arm) deemed unrelated by the principal investigator.

*received only 1 dose of zeto 30 mg

PALIZADE Safety Overview (Safety Population, N=84)

Treatment Exposure/Adverse Events	Zetomipzomib 30 mg N=27	Zetomipzomib 60 mg N=29	Placebo N=28
Participants reaching Week 13*, n (%) Participants reaching Week 25*, n (%)	18 (66.7) 13 (48.1)	18 (62.1) 12 (41.4)	20 (71.4) 14 (50.0)
Number of doses administered per participant, Mean, (SD)	16.3 (9.0)	13.8 (9.9)	18.1 (9.8)
Compliance†, Mean, (%)	97.7 (3.8)	97.2 (5.8)	97.9 (9.3)
Participants with at least 1 Treatment Emergent Adverse Event (TEAE), n (%)	23 (85.2)	25 (86.2)	17 (60.7)
Most common TEAEs: Systemic injection reaction (SIR), n (%) Injection site reaction (ISR), n (%)	 14 (51.9) 6 (22.2)	 20 (69.0) 13 (44.8)	 3 (10.7) 2 (7.1)
TEAE leading to study drug discontinuation, n (%)‡	4 (14.8)	4 (13.8)	1 (3.6)
Treatment Emergent Serious Adverse Event, n (%)	5 (18.5)	8§ (27.6)	3 (10.7)
Grade 3 or 4 TEAE, n (%)	4 (14.8)	8 (27.6)	3 (10.7)
Infectious TEAE, n (%)	13 (48.1)	11 (37.9)	13 (46.4)
Grade ≥3 Infectious TEAE¶, n (%)	2 (7.4)	3 (10.3)	0 (0)
Opportunistic Infections#, n (%)	0 (0)	0 (0)	0 (0)
Deaths, n (%)	2 (7.4)	1 (3.4)	1 (3.6)

*Defined as participants with evaluable response at Week 13 (or 25) visit.
†Compliance rate was calculated as the total number of injections administered divided by the number of injections planned.
‡Zeto 30 mg arm: Grade 3 systemic injection reaction (related, recovered), grade 3 community acquired pneumonia (related, recovered), grade 5 acute respiratory distress syndrome (related, fatal), grade 5 cardiac insufficiency (unrelated, fatal).
Zeto 60 mg arm: Grade 1 chills and fever (related, recovered), grade 3 lupus vasculopathy and acute pulmonary edema (unrelated, recovered), grade 2 decreased eGFR (related, recovered), grade 3 dengue fever and acute kidney failure (unrelated, recovered).
Placebo: Grade 5 cerebral ischemia and respiratory insufficiency (unrelated, fatal).
§Four participants randomized to zeto 60 mg arm but received zeto 30 mg before the TESAE (2 were after first dose).
¶Zeto 30 mg arm: Grade 3 pseudomonas infection (related, recovered), Grade 3 community acquired pneumonia (related, recovered with sequelae).
Zeto 60 mg arm: Grade 3 septic shock and Grade 4 urinary tract infection (both unrelated, recovered); Grade 3 unspecified bacterial pneumonia (related, recovered); Grade 3 dengue fever (unrelated, recovered).
#Opportunistic infections were evaluated by the sponsor through clinical assessment of reported infections.

Fatalities in PALIZADE and SIR Across Studies

Fatalities in PALIZADE

- All 4 fatalities occurred within first 3 months of treatment initiation.
- Rate of fatalities in PALIZADE (4.7%) consistent with other global studies in LN[1-13]
- Underlying disease parameters (e.g. nephrotic range proteinuria) present in all cases
- Systemic infection suspected in 2 fatalities occurring in Philippines based on laboratory values
- Patients in Philippines also displayed symptoms consistent with SIR.

Fatal events occurred in patients with suspected systemic infection at baseline and/or significant underlying comorbidities.

Integrated Summary of Systemic Injection Reactions (SIR) Across Studies (N=334)

- Constellation of symptoms including hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills
- Onset 8 – 24 hours after dosing, generally self-resolving within 48 hours
- The proportion of patients experiencing a SIR at weekly visits was highest at Week 0 (37%) and decreased over time to as low as 6%.
- Across studies, 54.7% of SIRs were Grade 1 and 38.4% were Grade 2.
- 8 subjects with a serious ≥Grade 3 SIRs
  - 5 subjects in PALIZADE (including 2 fatalities)
  - 3 subjects in MISSION LN patients

References: 1. Figueroa-Parra G et al, Arthritis Rheumatol. 2024;76(9):1408-1418. 2. Furie R et al. N Engl J Med. 2020;383(12):1117-1128.3. Rovin BH et al. Kidney Int 95(1): 219-231. 4. Rovin BH et al. The Lancet 397(10289): 2070-2080. 5. Mysler EF et al. Arthritis Rheum. 2013;65(9):2368-2379. 6. Furie R et al. N Engl J Med 2025;392:1471-1483 7. Saxena A et al. Arthritis Rheumatol. 2024;76(1):59-67. 8. Furie et al. 2021 EULAR Virtual Congress. 9. Rovin BH et al. Arthritis & Rheumatism 2012;64(4): 1215-1226. 10. Appel GB et al. J Am Soc Nephrol 2009;20(5): 1103-1112. 11. Dooley MA, et al. N Engl J Med. 2011;365(20):1886-1895. 12. Ginzler EM et al. Arthritis Res Ther. 2012 Feb 7;14(1):R33. 13. ACCESS Trial Group. Arthritis Rheumatol. 2014 Nov;66(11):3096–3104.

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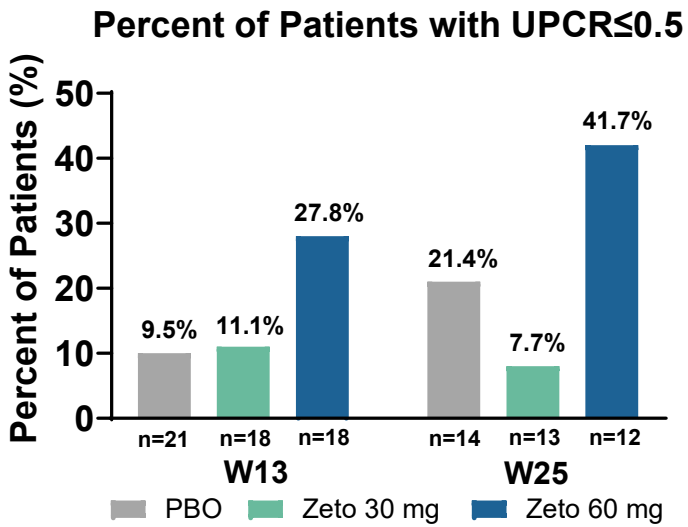
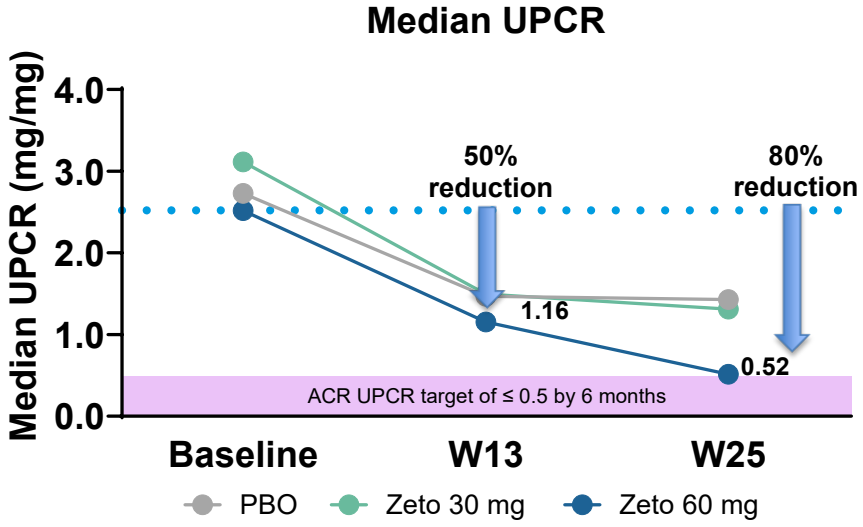
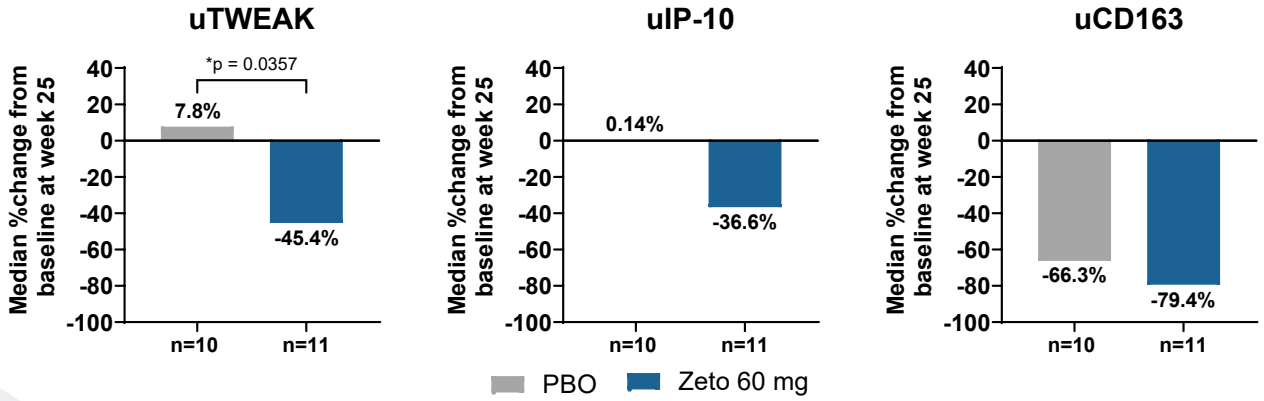
Rapid Proteinuria Reduction and Improvements in Key Urinary Biomarkers in Class III/IV ± V LN Patients Treated with Zetomipzomib 60 mg



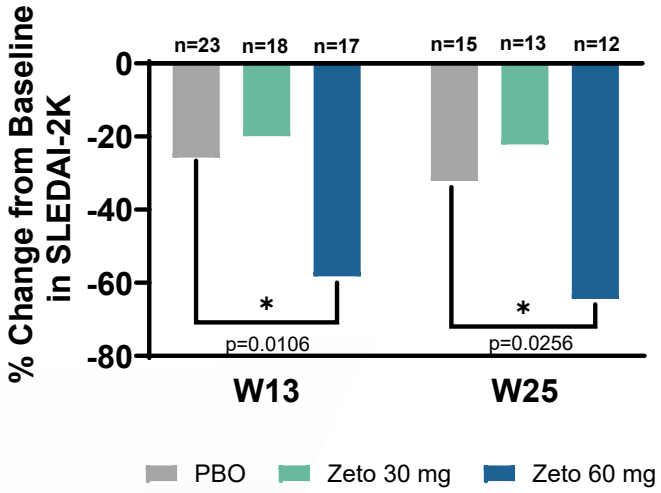


n = number of patients with evaluable response at the visit.



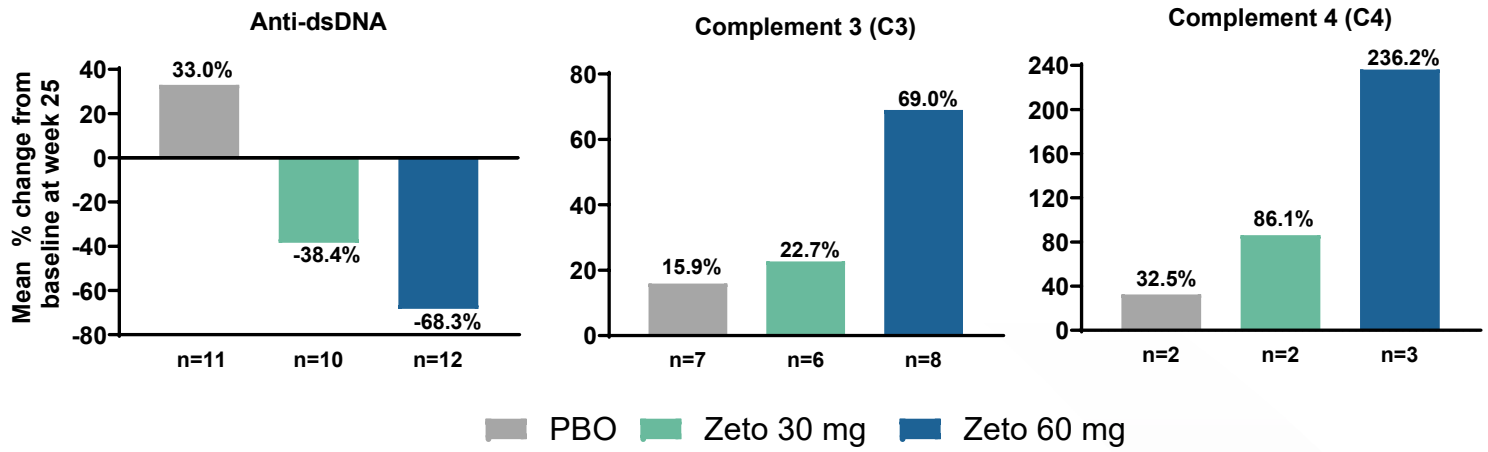
Zetomipzomib 60 mg Shows Greater Improvements in SLEDAI-2K and Serologic Markers of SLE at Week 25

SLEDAI-2K



n = number of patients with evaluable response at the visit

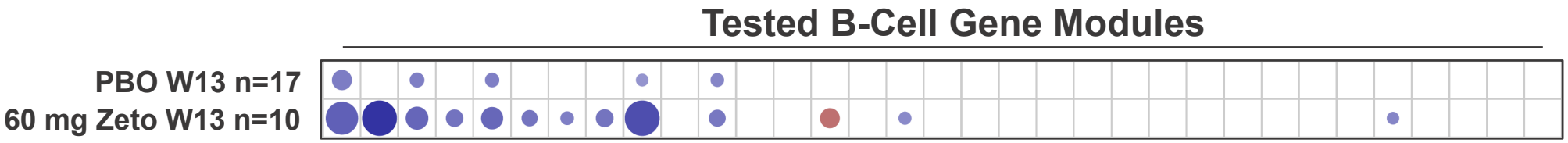
Serologic Biomarkers

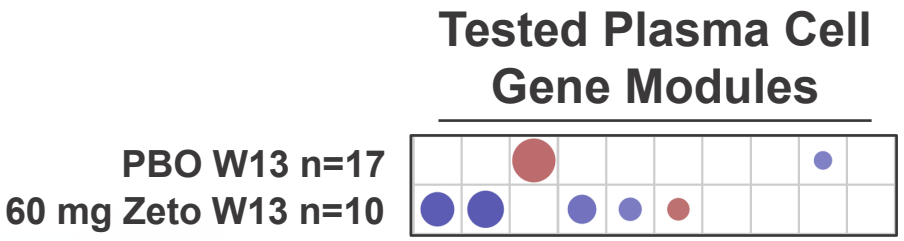


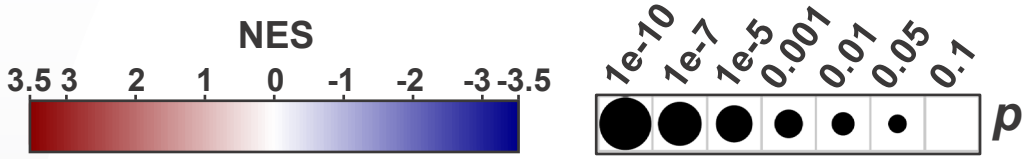
n = patients with abnormal levels at baseline who had an evaluable response at the visit.

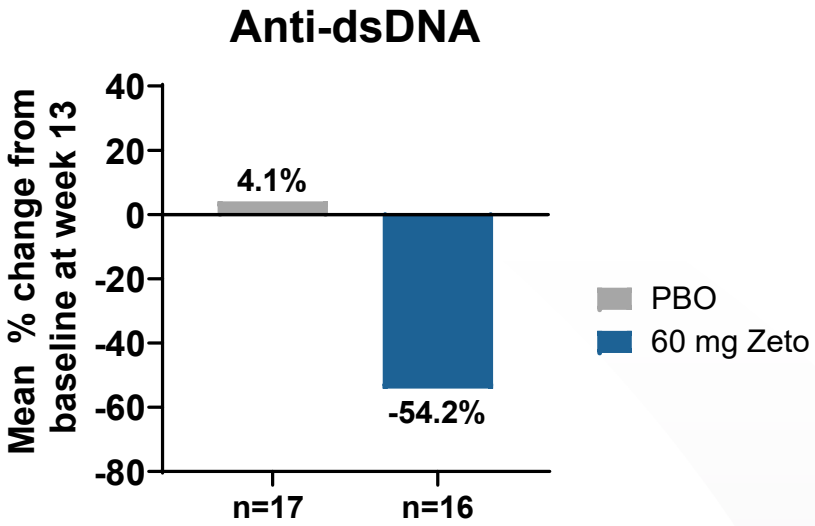
Abbreviations: dsDNA, double-stranded DNA; PBO, placebo; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; W, week; Zeto, zetomipzomib.

Zetomipzomib Decreases B-cell and Plasma Cell Gene Expression Modules at Week 13 Corresponding to Lowered Anti-dsDNA Antibodies









n = patients with abnormal levels at baseline who had an evaluable response at the visit.

Summary/Conclusion

- Analysis of safety data indicates an overall similar profile between zetomipzomib 30 mg and 60 mg.
- The rates of infectious AEs were similar between zetomipzomib and placebo.
- Fatalities occurred in the presence of severe baseline disease and/or signs of suspected systemic infections, confounding assessment of any potential contribution of zetomipzomib.
- Data from this study showed encouraging preliminary clinical activity of zetomipzomib 60 mg at Week 25, with more than 40% of participants achieving a UPCR ≤0.5, along with improvements in key urinary biomarkers in LN, serologic markers, and SLEDAI-2K scores.
- Kezar assessment of PALIZADE safety and efficacy data to date and data from >300 patients across multiple trials support continued development of zetomipzomib in lupus nephritis and other autoimmune diseases.

Acknowledgements

- With deep appreciation to the patients, caregivers, investigators, and study site personnel whose commitment made this study possible.