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

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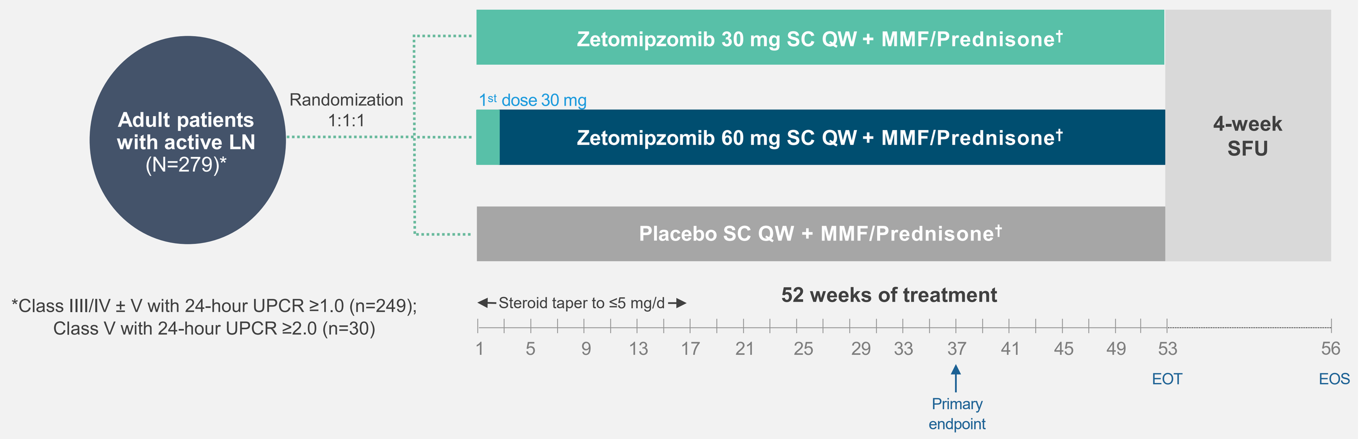
Introduction

- Zetomipzomib (zeto), a selective immunoproteasome inhibitor, has previously shown anti-inflammatory activity in patients (pts) with SLE and LN in the open-label MISSION trial (NCT03393013)[1,2].
- The PALIZADE trial (NCT05781750)[3] was a global Phase 2b, multi-center, randomized (1:1:1), controlled, double-blind trial comparing the efficacy and safety of weekly subcutaneous administration of zeto 30 mg or 60 mg with placebo (PBO) in pts with active LN (Class III or IV ± V and pure Class V) on background standard-of-care therapy of mycophenolate mofetil (MMF) or equivalent plus corticosteroids.
- An Independent Data Monitoring Committee recommended pausing enrollment and dosing following 4 fatalities (1 - PBO, 2 - 30 mg zeto arm, 1 - 60 mg zeto arm [received only 1 dose of zeto 30 mg]) and additional nonfatal treatment-emergent serious adverse events (TESAE) with common manifestations or proximity to dosing.
- PALIZADE was subsequently terminated early by the sponsor for strategic business reasons.

Methods

- Planned enrollment was 279 patients, including 249 with proliferative LN (Class III or IV ± V) with a planned duration of 52 weeks of treatment and a primary endpoint at Week 37.
- A total of 84 patients enrolled prior to study termination, including 74 with Class III/IV ± V disease who comprise the intention-to-treat population for efficacy results.
- At the time of termination, 39 patients with Class III or IV ± V disease had reached Week 25 for UPCR evaluation. Of these, 16 had received a dose within ≤9 days prior to their Week 25 visit (6 on placebo, 5 on 60 mg zeto arm, and 5 on 30 mg zeto arm), and no patients had completed the full 52 weeks of treatment. The n values in the figures denote the number of patients with an evaluable response at the visit.
- Data from the intention-to-treat population encompassing proteinuria changes, median UPCR and serologic markers (anti-dsDNA antibodies, C3/C4) at Weeks 13 and 25 are presented here.
- Due to early termination of the study, enrollment was insufficient to support formal hypothesis testing; results are primarily descriptive, with p-values provided for context where appropriate.

Figure 1. PALIZADE Study Design



†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 g)

Key Demographics and Baseline Characteristics (N=84)

- Patients: N=84 randomized (PBO n=28; zeto 30 mg n=27; zeto 60 mg n=29).
- Mean age 32.1 y (SD 9.6); 92.9% female.
- Region: Asia Pacific 56.0%, Latin America 33.3%, EMEA 6.0%, North America 4.8%
- Race/Ethnicity: Asian 56.0%, White 26.2%, American Indian/Alaskan Native 9.5%, Black/African American 6.0%, Other 2.4%; Hispanic/Latino 33.3%.
- Disease history: Mean SLE duration 6.5 y (SD 5.8); LN duration 3.7 y (SD 4.5).
- LN class (ISN/RPS): IV only 41.7%, III only 20.2%, III+V 13.1%, IV+V 13.1%, Pure V 11.9%.
- Baseline activity/renal: Mean SLEDAI-2K 11.3 (SD 5.2); 24-hr UPCR 3.5 mg/mg (SD 1.9); eGFR 108.0 mL/min/1.73 m² (SD 29.8).
- Background therapy: MMF 100%, oral prednisone 98.8%, IV methylprednisolone 81.0%, antimalarial 86.9% (e.g., hydroxychloroquine).

Results

Table 1. PALIZADE Safety Overview (Safety Population), N=84

Treatment Exposure/Adverse Events	Zeto 30 mg N=27	Zeto 60 mg N=29	PBO N=28
Patients reaching Week 13*, n (%) Patients 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 patient, 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)
Patients 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)

- Mean immune cell counts or immunoglobulin levels were not reduced to below lower limit of normal in either zetomipzomib treatment arm.

*Defined as patients 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.
‡Four patients 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.

Table 2. Summary of Reported Fatal Events (N=4)

Patient Demographics/ Country	Treatment arm/ Time on Tx /No. of Doses	Cause of Death	Confounding Factors
30F, Asian, LN Class III Philippines	60 mg zeto 2 Days/1 dose (assigned 60 mg but only received 30 mg)	Dehydration, hypovolemic shock	Evidence of early UTI at baseline, diarrhea followed, procalcitonin level >1,000× ULN at 24h → severe sepsis/septic shock suspected
27F, Asian, LN Class IV Philippines	30 mg zeto 9 Days/2 doses	Acute respiratory distress syndrome	Baseline ↑ liver enzymes, anemia and peripheral smear abnormalities, baseline CRP>20xULN (screening CRP 2.6x ULN) → systemic infection with coagulopathy/DIC suspected (markedly elevated procalcitonin day 8)
40F, White, LN Class IV Argentina	30 mg zeto 80 Days/ 12 doses	Cardiac failure	Signs of pre-existing untreated pulmonary hypertension on echo, possibly due to chronic thromboembolic disease, suspected antiphospholipid syndrome and pulmonary embolus
56F, White, LN Class V Argentina	PBO 19 Days/ 4 doses	Cerebral ischemia, respiratory failure	Nephrotic range proteinuria, hypoalbuminemia

Results (cont'd)

Figure 2. Rapid Proteinuria Reduction Observed in Class III/IV ± V Patients Treated with Zetomipzomib 60 mg

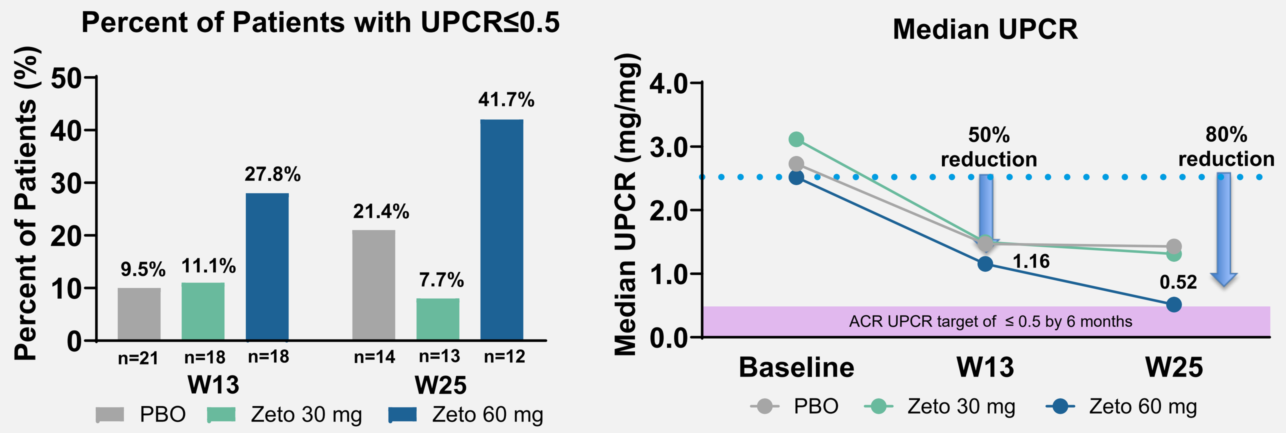


Figure 3. Zetomipzomib 60 mg Shows Greater SLEDAI-2K Reduction vs Placebo

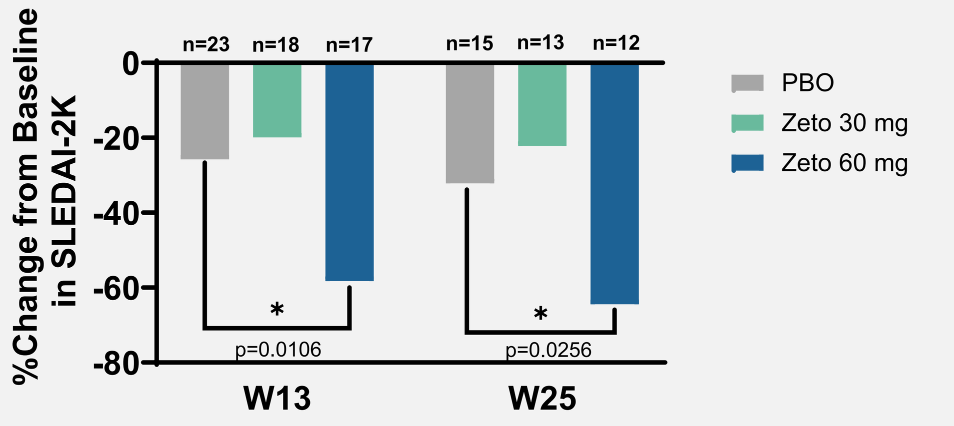
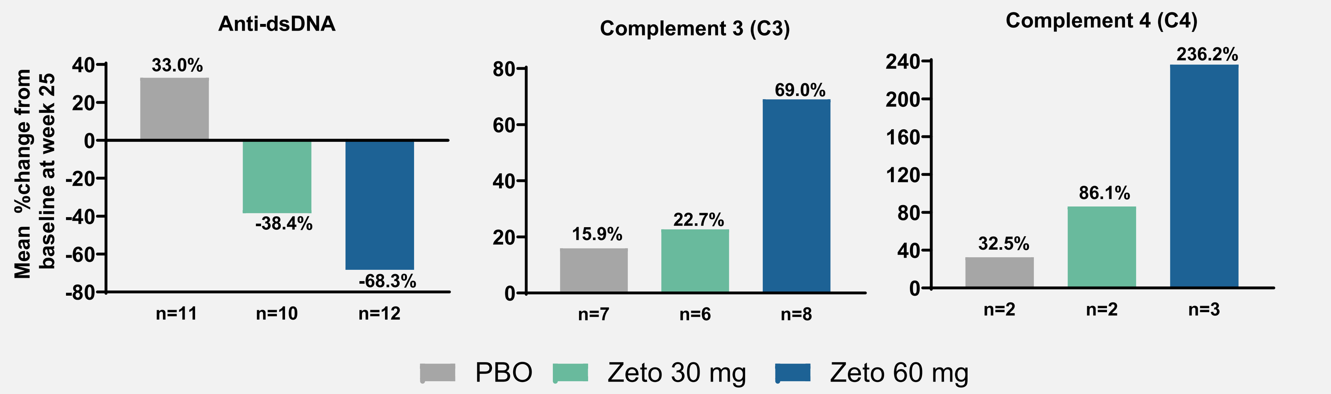
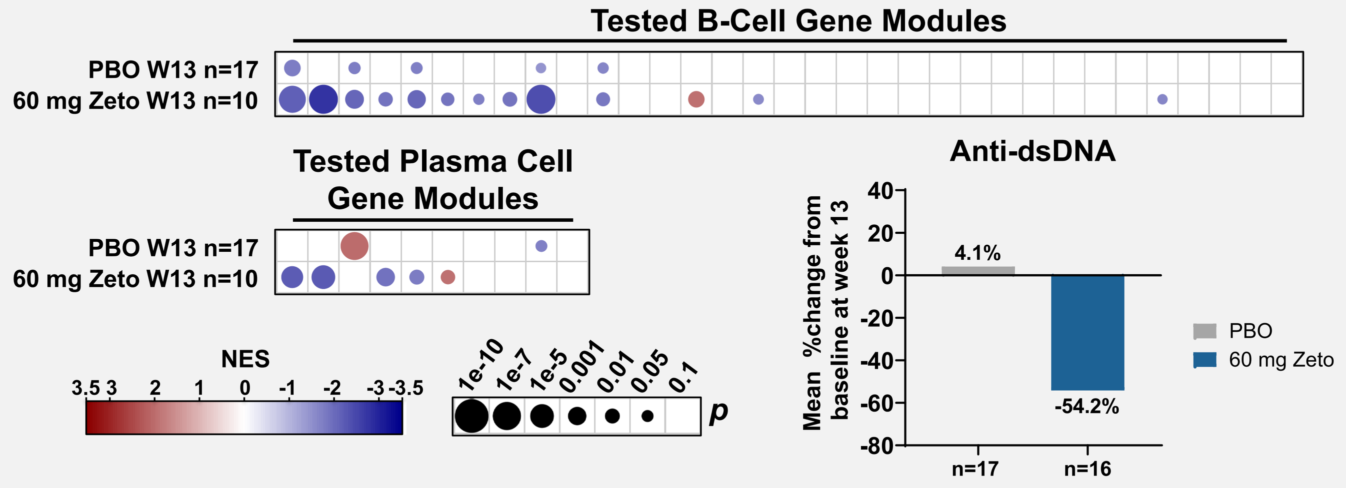


Figure 4. Zetomipzomib 60 mg Demonstrates More Pronounced Improvements in Serologic Markers of SLE at Week 25 in Patients With Abnormal Levels at Baseline



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

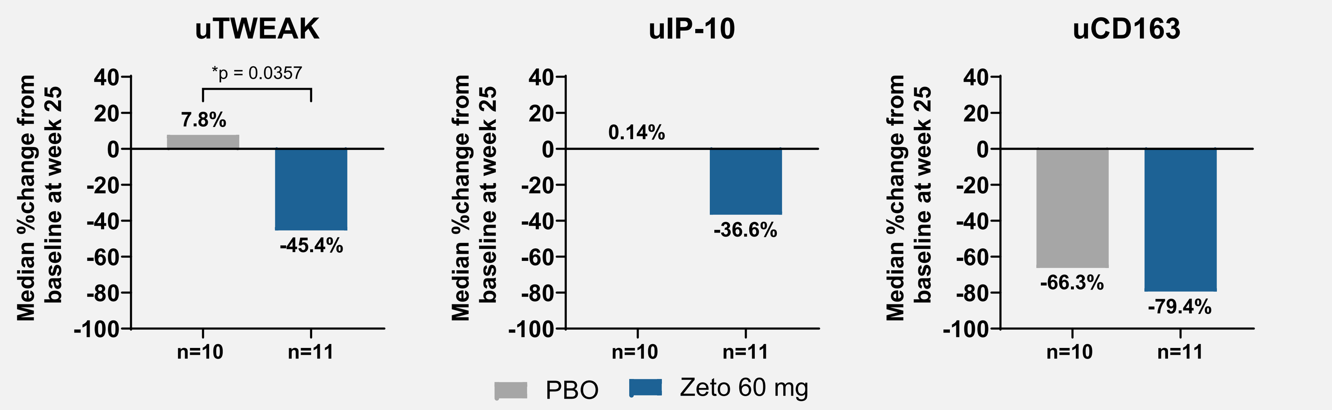
Figure 5. Zetomipzomib Decreases B-cell and Plasma Cell Gene Expression Modules at Week 13 Corresponding to Lowered Anti-dsDNA Antibodies



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

Results (cont'd)

Figure 6. Zetomipzomib Reduces Key Urinary Biomarkers in LN



Summary

Safety

- Most common AEs were ISR (98% were Grade 1 or 2) and SIRs (86% were Grade 1 or 2).
- Fatal events (4 total: 1 PBO, 2 zeto at 30 mg, 1 zeto at 60 mg [assigned 60 mg but only received 30 mg]) occurred in patients with suspected systemic infection at baseline and/or significant underlying comorbidities (e.g., cardiovascular disease, antiphospholipid syndrome).
- No opportunistic infections or clinically meaningful changes in mean immune cell/immunoglobulin levels were observed.
- Similar safety profile between zeto 30 mg and 60 mg arms and a profile consistent with the MISSION study and LN patient population.

Efficacy

- A greater proportion of patients in the zeto 60 mg treatment arm (5/18 [27.8%]) demonstrated a decrease in UPCR to ≤0.5 compared to patients in the zetomipzomib 30 mg treatment arm (2/18 [11.1%]) and the PBO treatment arm (2/20 [10%]) at Week 13.
- Encouraging clinical activity was observed in patients reaching Week 25, with >40% achieving a median UPCR ≤0.5 and improvements in serologic markers among those receiving zetomipzomib 60mg.
- eGFR improved across all groups, with the greatest % increase at Week 25 from baseline in the 60 mg cohort (+12.1%) versus 30 mg (+6.1%) and placebo (+2.3%).

Conclusions

- **Zetomipzomib 60 mg resulted in increased rates of improvements in proteinuria and symptomatic and serologic improvements in SLE.**
- **Similar safety profile between zetomipzomib 30 mg and 60 mg**
- **The rates of infectious AEs were similar between zetomipzomib and placebo.**
- **Safety data for zetomipzomib is consistent with other global studies in LN including SAEs and fatalities[4-16].**
- **Fatalities occurred in the presence of severe baseline disease and/or signs of suspected systemic infections, confounding assessment of any potential contribution of zetomipzomib.**
- **The PALIZADE study highlights the potential of zetomipzomib 60 mg to provide clinically meaningful activity in lupus nephritis.**

Author Disclosures and Acknowledgements

RF is a consultant and investigator for Kezar. NKA, SD, EL, TM, KP, RP, KR, ZT, and JAW are employees and shareholders of Kezar. **RLL** is a consultant and shareholder of Kezar.

Abbreviations: CRP, C-reactive protein; CRR, complete renal response; eGFR, estimated glomerular filtration rate; EMEA, Europe, Middle East, and Africa; EOS, end of study; EOT, end of treatment; IV, intravenous; MMF, mycophenolate mofetil; PBO, placebo; SC, subcutaneous; SFU, safety follow-up; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TX, treatment; UPCR, urine protein-to-creatinine ratio; UTI, urinary tract infection.

References: 1. Furie et al. 2021 ACR Convergence. 2. Saxena et al. 2022 ACR Convergence. 3. Clinicaltrials.gov Accessed September 17, 2025. https://clinicaltrials.gov/ct2/show/NCT05781750 4. Figueroa-Parra G et al, *Arthritis Rheumatol.* 2024;76(9):1408-1418. 5. Furie R et al. *N Engl J Med.* 2020;383(12):1117-1128.6. Rovin BH et al. *Kidney Int* 95(1): 219-231. 7. Rovin BH et al. *The Lancet* 397(10289): 2070-2080. 8. Mysler EF et al. *Arthritis Rheum.* 2013;65(9):2368-2379. 9. Furie R et al. N Engl J Med 2025;392:1471-1483 10. Saxena A et al. *Arthritis Rheumatol.* 2024;76(1):59-67. 11. Furie et al. 2021 EULAR Virtual Congress. 12. Rovin BH et al. *Arthritis & Rheumatism* 2012;64(4): 1215-1226. 13. Appel GB et al. *J Am Soc Nephrol* 2009;20(5): 1103-1112. 14. Dooley MA, et al. *N Engl J Med.* 2011;365(20):1886-1895. 15. Ginzler EM et al. *Arthritis Res Ther.* 2012 Feb 7;14(1):R33. 16. ACCESS Trial Group. *Arthritis Rheumatol.* 2014 Nov;66(11):3096–3104.

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