Zetomipzomib, a First-in-Class Selective Immunoproteasome Inhibitor, Demonstrates Steroid Sparing Biochemical Remission in Patients with Relapsed or Insufficiently Responding Autoimmune Hepatitis in a Randomized, Double-blind, Placebo-controlled, Phase 2a Study

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Disclosures

- Consultant and Investigator for Kezar Life Sciences
- Consultant Amgen, Eli Lilly, RegCell, Mirum
- Executive Director, Autoimmune Hepatitis Association

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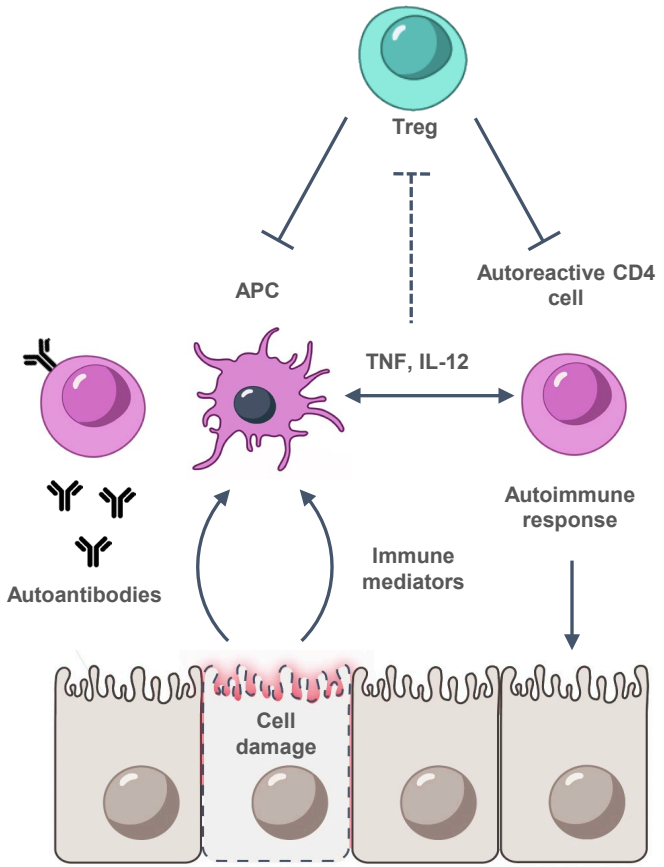
Zetomipzomib Has Potential to Modulate Multiple Immune Pathways Underlying Autoimmune Hepatitis

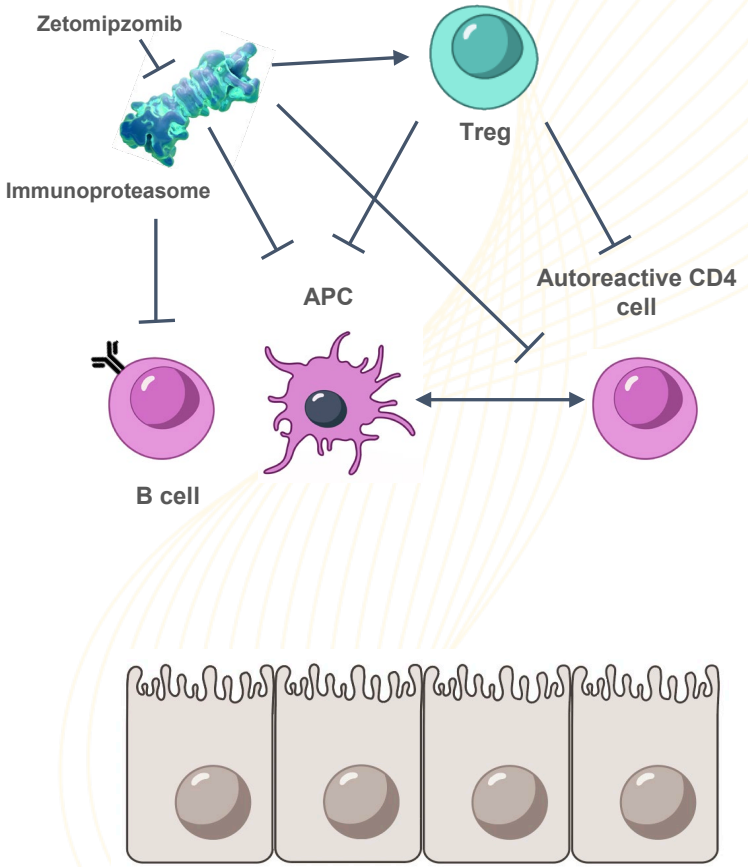
Cellular Dysfunction Observed in AIH



Significant Unmet Needs in AIH

- Long-term corticosteroids and immunosuppressants remain standard to achieve and maintain remission
- 30 – 50% fail to achieve remission, flare, or are intolerant to standard of care treatment[1-6]
- Chronic corticosteroid use increases health risks and decreases quality of life for patients[2]
- >5-fold risk of liver failure or liver related death in patients who do not achieve a complete remission by 6 months[7]

Zetomipzomib Targets Multiple Immune Effector Cells Involved in Autoimmunity



References: 1. Ergenc I et al. *Gastroenterol Hepatol (NY)*. 2025;21(3):152-160. 2. European Association for the Study of the Liver. *J Hepatol*. 2025;83(2):453-501. 3. Schregel I et al. *Liver Int*. 2024;44(10):2687-2699. 4. Pape S et al. *J Hepatol*. 2022;76(4):841-849. 5. Heneghan MA, Lohse AW. *J Hepatol*. 2025;82(5):926-937. 6. Mack CL et al. *Hepatology*. 2020;72(2):671-722. 7. Slooter CD et al. *Hepatology*. 2024;79(3):538-550.

Treatment Goals Are Focused on Biochemical Normalization and Low Daily Steroid Dose

	AASLD[1]	EASL[2]
Biochemical Remission Criteria	ALT, AST, & IgG normalization by 6 months	ALT, AST, & IgG normalization by 6 months
Steroid Dose	Prednisone 20-40 mg/d with taper to ≤5-10 mg/d	0.5-1 mg/kg/d prednis(ol)one with taper to ≤5 mg/d
Immunosuppressant Therapy	Azathioprine 50-150 mg/d	Azathioprine 1-2 mg/kg/d or MMF 1.5-2 g/d

- *No medications specifically to treat AIH approved by the FDA*
- *Standard-of-care first line treatment has remained largely unchanged since adoption more than 40 years ago*
- *No strongly supported regimens for patients who are refractory to initial therapy; current guidelines recommend tapering steroids to ≤5-10 mg/day*

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EASL, European Association for the Study of the Liver; IgG, Immunoglobulin G.

References: 1. Mack CL et al. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance from the American Association for the Study of Liver Diseases (AASLD). Hepatology. 2020;72(2):671-722. doi: 10.1002/hep.3106. 2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune Hepatitis. J Hepatol. 2025 May 10:S0168-8278(25)00173-4. doi: 10.1016/j.jhep.2025.03.017. Epub ahead of print. PMID:40348684.

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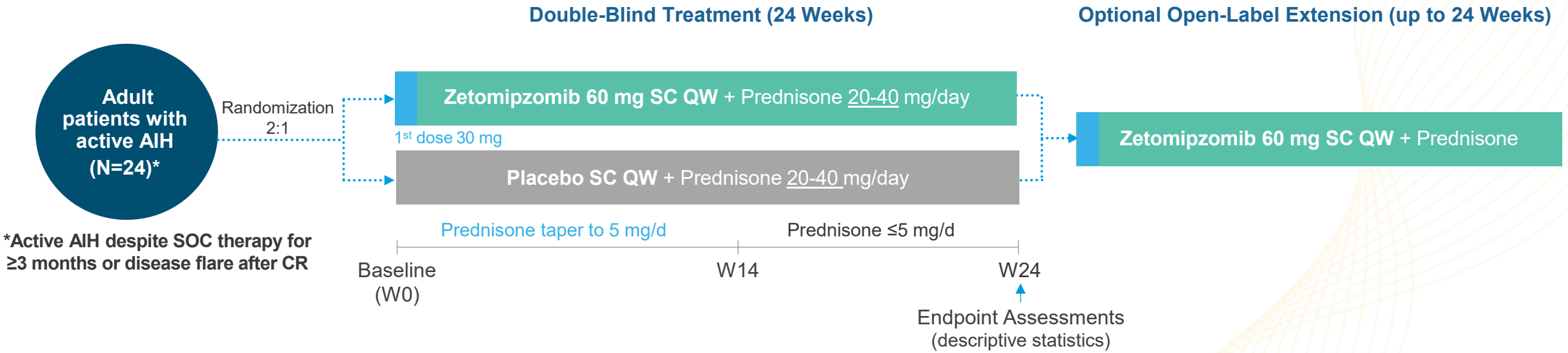
PORTOLA: Evaluate the Safety and Efficacy of Zetomipzomib in Relapsed or Insufficiently Responding AIH



Key Inclusion Criteria

- Screening ALT values 1.25-10x ULN
- Liver biopsy results with Ishak score[1] (modified HAI) ≥5 (18 max) indicating active AIH, from a biopsy performed at screening or within 6 months prior to screening
- Mild or no hepatic impairment (Child-Pugh category A)

Endpoints (descriptive in nature)

- **Primary Efficacy:** Proportion of patients with complete biochemical response (CR) by W24, defined as normalized ALT, AST, and IgG (if elevated at baseline) with steroid dose ≤ baseline
- **Primary Safety**: Proportion of patients who experience AEs and SAEs
- **Key Secondary:** Proportion of patients who achieve CR and successful glucocorticoid taper (10 mg) by W24
- **Exploratory:** Change from baseline in Ishak score (mHAI); Glucocorticoid Toxicity Index; PROMs

Key Stratification

- **Patients entering the study (screening period) on steroid-based therapy**

References: 1. Ishak K et al. J Hepatol. 1995 June;22(6):696-9; https://clinicaltrials.gov/ct2/show/NCT05569759.
Abbreviations: AE, adverse event; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, complete response; HAI, histological Activity Index; IgG, Immunoglobulin G; PROM, Patient-Reported Outcome Measure; QW, once weekly; SAE, serious adverse event; SC, subcutaneous; SOC, standard of care; W, week.

PORTOLA: Demographics and Baseline Characteristics

ITT Population (N=24)

	Placebo N=8	Zetomipzomib N=16	Total N=24
Age, median (min, max), years	54.0 (26, 72)	59.0 (25, 75)	57.5 (25, 75)
Female, n (%)	6 (75.0)	8 (50.0)	14 (58.3)
Race, n (%)			
White	7 (87.5)	13 (81.3)	20 (83.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (12.5)	2 (12.5)	3 (12.5)
AIH duration, median (min, max), years	6.7 (0.4, 21.3)	3.4 (0.2, 19.7)	5.0 (0.2, 21.3)
Time from biopsy to baseline, median (min, max), weeks	3.0 (2.1, 26.7)	8.5 (1.0, 34.1)	3.9 (1.0, 34.1)
Ishak score, median (min, max)	8.0 (5, 13)	7.0 (5, 12)	7.0 (5, 13)
Liver stiffness, median (min, max), kPa	9.2 (5, 49)	11.2 (3, 75)	10.0 (3, 75)

	Placebo N=8	Zetomipzomib N=16	Total N=24
Antibodies			
ANA positive, n (%)	6 (75.0)	14 (87.5)	20 (83.3)
SMA positive, n (%)	4 (50.0)	8 (50.0)	12 (50.0)
LKM-1 positive, n (%)	0 (0)	0 (0)	0 (0)
LC-1 positive, n (%)	1 (12.5)	0 (0)	1 (4.2)
SLA, median (min, max)	2 (1, 116.1)	3 (1.4, 118.9)	3 (1, 118.9)
Laboratory values, median (min, max)			
ALT (U/L)	115.3 (46.5, 258.5)	106.3 (38, 220)	108.5 (38.0, 258.5)
AST (U/L)	95.0 (59.5, 187.0)	63.5 (30.5, 225.0)	76.3 (30.5, 225.0)
IgG (mg/dL) in those with elevated IgG at baseline	(n=5) 2015 (1765, 2960)	(n=9) 2185 (1620, 3880)	(n=14) 2100 (1620, 3880)
ALP (U/L)	84 (27, 143)	108 (74, 202)	95 (27, 202)
Bilirubin, total (umol/L)	9 (4.6, 27.9)	9 (2.6, 21.9)	9 (2.6, 27.9)
Bilirubin, direct (umol/L)	3 (3.4, 7.9)	3 (3.4, 9.7)	3 (3.4, 9.7)
Albumin (g/L)	41 (0.04, 49)	42 (36, 48)	42 (0.04, 49)
PT/INR ratio	1 (0.9, 1.2)	1 (0.9, 1.3)	1 (0.9, 1.3)

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*ITT Population (N=24) includes all randomized patients.

Reference ranges: ALP normal range female= 30-115 U/L; ALP normal range male= 43-115 U/L; ALT normal range female= 10-33 U/L; ALT normal range male= 10-40 U/L; AST normal range female= 10–36 U/L; AST normal range male= 10-43 U/L; Total bilirubin normal range= up to 18.8 umol/L; Direct Bilirubin normal range= 0-6.8 umol/L; IgG normal range= 767 – 1590 mg/dL; PT/INR ratio normal range= 0.9-1.1.

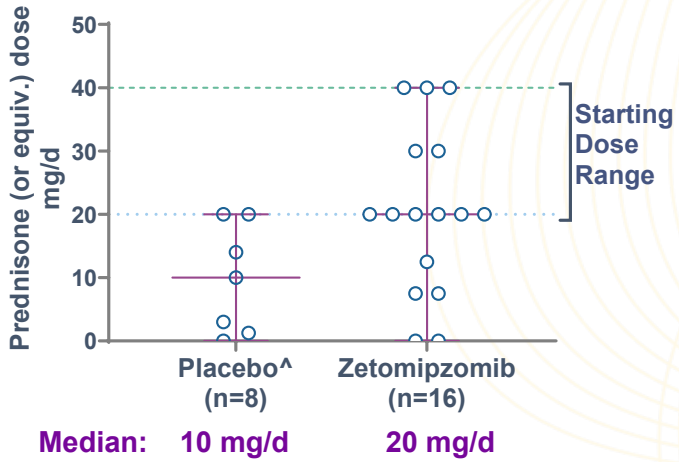
Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; IgG, immunoglobulin G; ITT, intent-to-treat; LC-1, liver cytosol type 1 antibody; LKM-1, liver kidney microsomal antibodies; PT/INR, prothrombin time/international normalized ratio; SMA, smooth muscle antibody; SLA, soluble liver antigen.

PORTOLA: Demographics and Baseline Characteristics – Cont'd
ITT Population (N=24)

	Placebo* N=8	Zetomipzomib N=16	Total N=24
Concomitant medications at baseline*			
Prednisone (or equivalent)* n (%)	7 (87.5)	16 (100)	23 (95.8)
Prednisone (or equivalent)†, dose in mg/day, median (min, max)	20 (20, 20)	20 (20, 30)	20 (20, 30)
Azathioprine, n (%)	3 (37.5)	4 (25.0)	7 (29.2)
Azathioprine dose in mg/d, median (min, max)	50 (50, 50)	75 (50, 150)	50 (50, 150)
Mycophenolate mofetil or mycophenolic acid, n (%)	1 (12.5)	9 (56.3)	10 (41.7)
Tacrolimus, n (%)	1 (12.5)	3 (18.8)	4 (16.7)
Cyclosporine, n (%)	1 (12.5)	0 (0)	1 (4.2)
# of patients receiving >1 immunosuppressant, n (%)	1 (12.5)	2 (12.5)	3 (12.5)
# of patients without any immunosuppressant, n (%)	3 (37.5)	2 (12.5)	5 (20.8)

- All patients were required to have a starting steroid dose of 20 mg/d prednisone (or equivalent) at baseline
- 63% of placebo patients vs 31% of zetomipzomib patients had steroid dose **raised** to 20 mg/d at baseline from screening

Corticosteroid Use at Screening



- 21 of 24 patients entered screening period on steroid-based therapy

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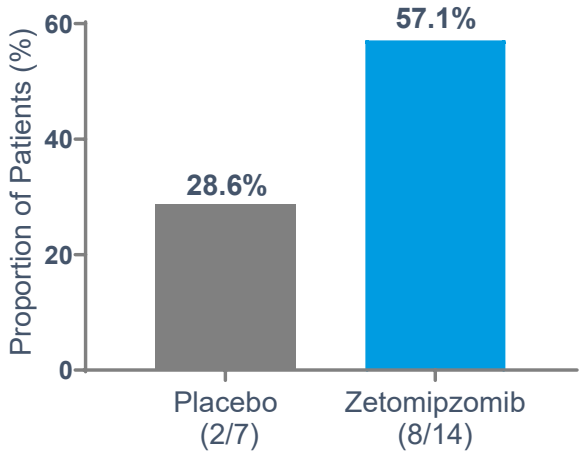
ITT Population (N=24) includes all randomized patients.
*Concomitant medications at baseline were not captured for 1 patient randomized to placebo but not dosed.
†The following glucocorticoid doses are approximately equivalent to 20 mg of prednisone:
budesonide 6 mg, methylprednisolone 16 mg, and prednisolone 20 mg.
^One placebo patient randomized but not dosed.

Zetomipzomib Treatment Induces Steroid-Free Biochemical Remissions

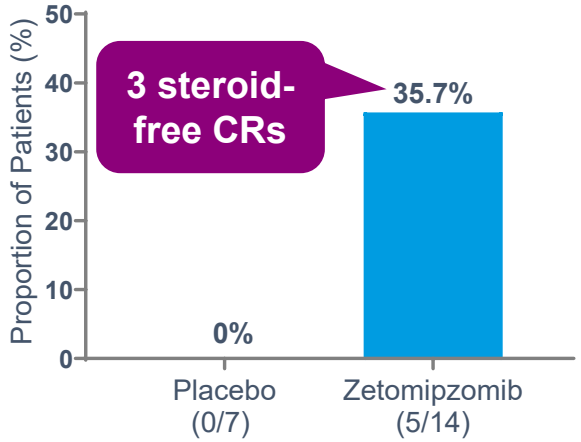
Prespecified Subset Analysis (N=21)

All Complete Responses (CR)



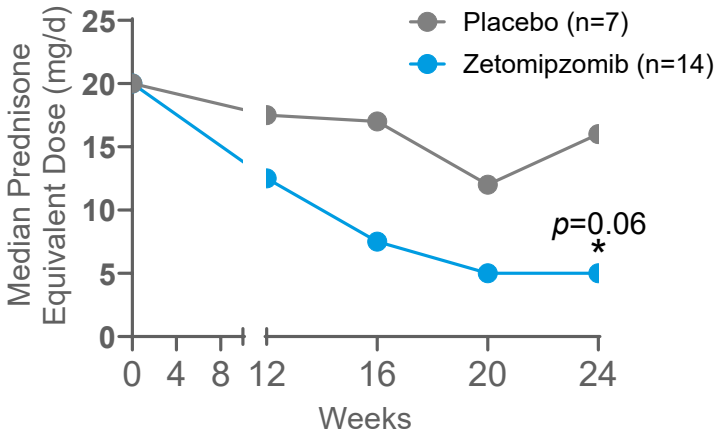
AASLD and EASL Guidelines Target Treatment Goals

CR with Steroid Taper to ≤5 mg/d



Zeto achieves lower steroid doses in relapsed/refractory AIH patients

Median Corticosteroid Dose Over Time



- ***Median duration of response of 8 zetomipzomib CRs is 27.3 weeks***
- ***No disease flares in any patient achieving CR on zetomipzomib during study, including OLE***

*ITT Population (N=24) includes all randomized patients. Prespecified subset analysis (N=21) includes ITT population entering study on steroid-based therapy.
Complete Response: Normal ALT, AST, and IgG values (if IgG level is elevated at Baseline) with glucocorticoid dose not higher than starting dose (at Baseline).
ALT normal range female= 10-33 U/L; ALT normal range male= 10-40 U/L; AST normal range female= 10–36 U/L; AST normal range male= 10-43 U/L; IgG normal range= 767 – 1590 mg/dL.
Statistical Analysis: *Wilcoxon rank-sum test
Abbreviations: CR, complete response; OLE, open label extension.

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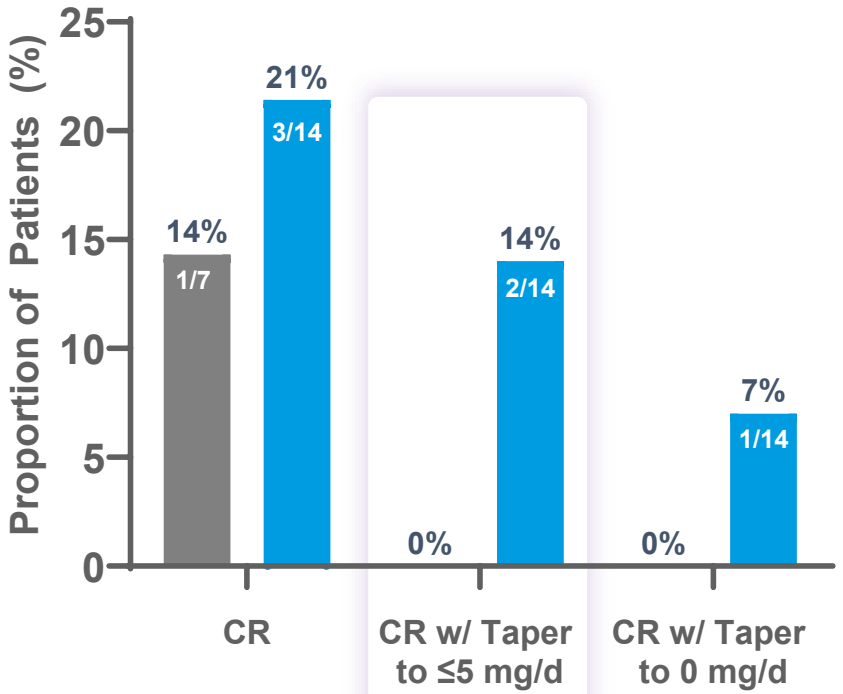
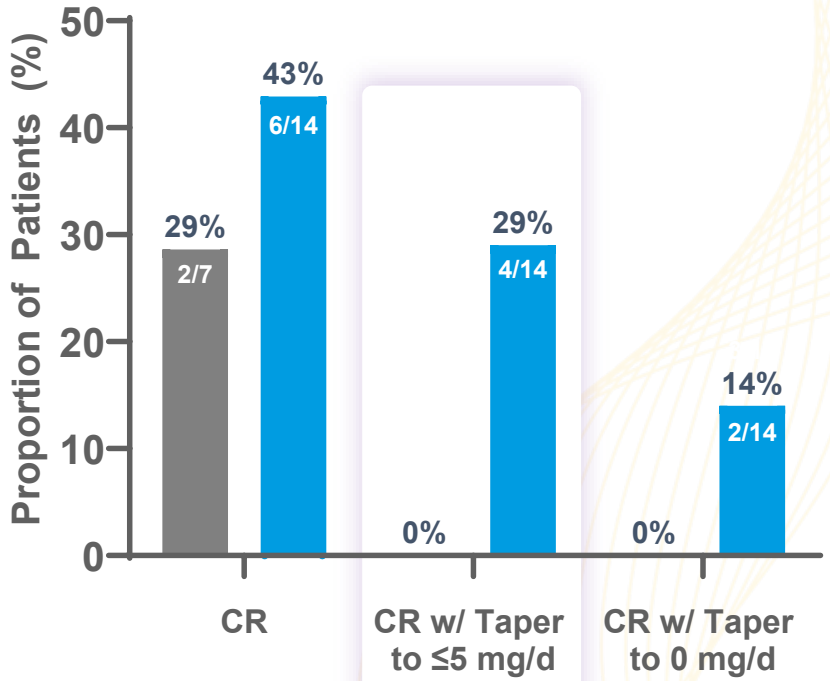
Histologic Improvement and Remission Are Observed with Zetomipzomib at W24

Prespecified Subset Analysis (N=21)

Histologic Remission (mHAI <4)



Histologic Improvement (≥2 points in mHAI)



Placebo (n=7)

Zetomipzomib (n=14)

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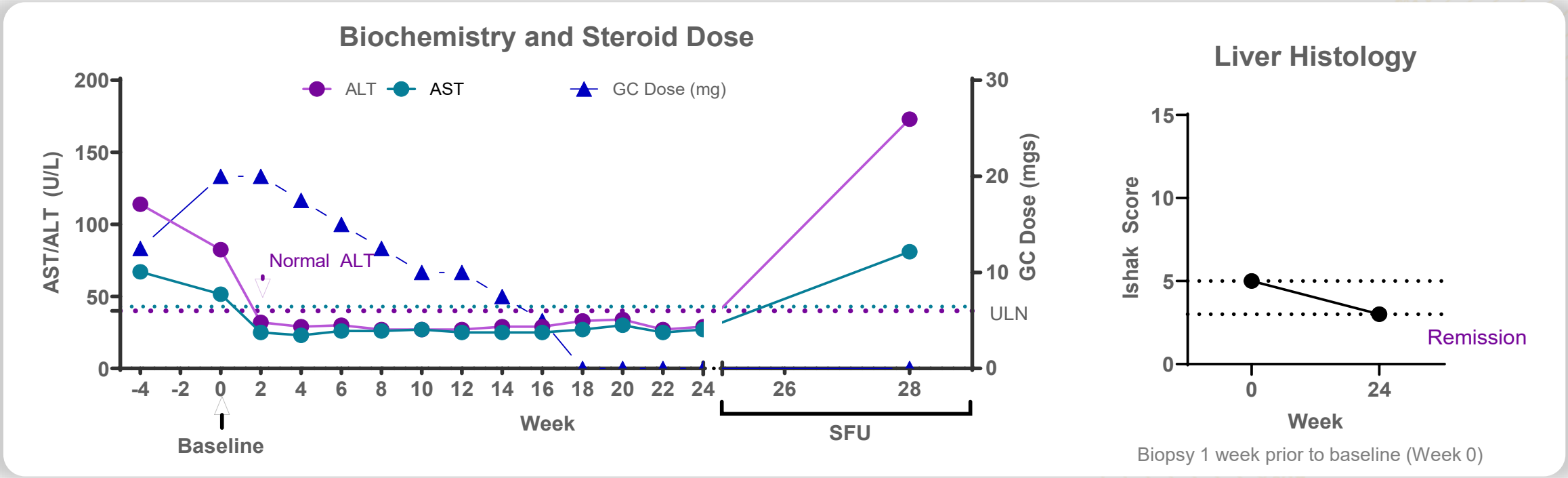
Abbreviation: CR, complete response; mHAI, modified Histology Activity Index.

PORTOLA Patient Journey

67 y/o white male, AIH since 2021 (2.8 years), ANA+, normal IgG and receiving MMF 1.5 g/day + Prednisone 20 mg at Baseline

PORTOLA Results

- Steroid free CR → Ineligible for OLE (Partial Hold) and flared by Week 28
- Histologic Remission
- Liver Stiffness (Elastography): 25% improvement at Week 24 (Baseline: 10.3 → 7.7 kPa)

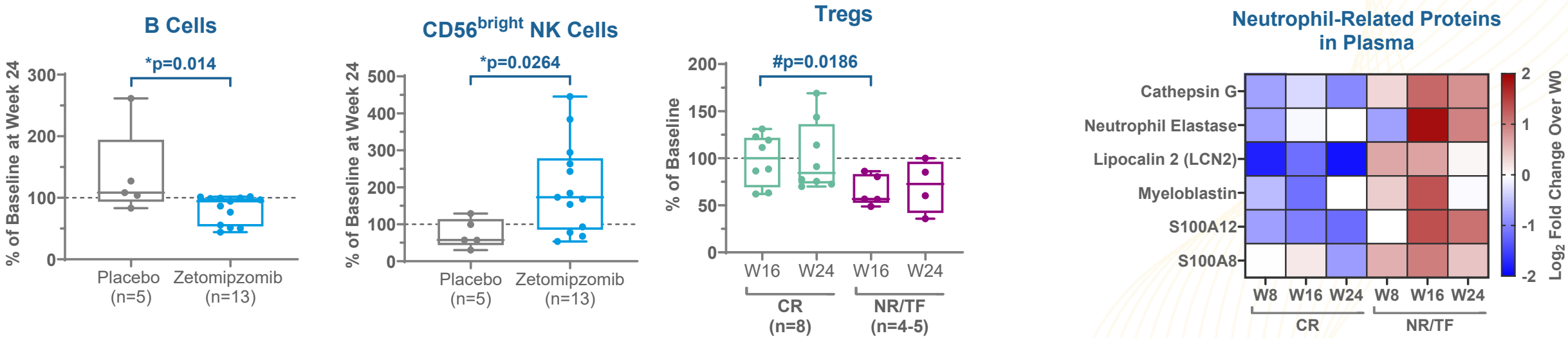


ALT ULN=40 U/L; AST ULN=43 U/L; IgG ULN=1590 mg/dL

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CR, complete response; GC, glucocorticoid; IgG, Immunoglobulin G; MMF, mycophenolate mofetil; OLE, open label extension; ULN, upper limit normal; SFU, safety follow-up.

Zetomipzomib Treatment Demonstrates Alterations in Biomarker Activity Correlating With Clinically Relevant Biochemical Responses in AIH

- Decreased B cell populations and increased CD56^{bright} NK cell populations are detected
- Elevated Tregs and reduced neutrophil-related proteins are observed in CR patients treated with zetomipzomib
- Innate and adaptive transcriptomic changes correspond to cellular and proteomic changes



Poster 4426: Analysis of Circulating Biomarkers in the Randomized, Double-Blind, Placebo-Controlled PORTOLA Phase 2a Study Evaluating Zetomipzomib, a Selective Immunoproteasome Inhibitor, in Patients with Autoimmune Hepatitis

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Complete Response: Normalization of ALT, AST, and IgG (if elevated at baseline) with no increase in glucocorticoid dose above baseline.
Treatment Failure: ALT or AST ≥2× baseline for ≥1 week, or need to increase steroids above baseline or add an immunosuppressant (unless due to a non-AIH adverse event).
Statistical Analyses: *Wilcoxon matched-pairs signed-rank test; #Wilcoxon rank-sum (Mann-Whitney U) test
Abbreviations: CR, complete response; NK, natural killer; NR, non-responder; TF, treatment failure; Treg, regulatory T cells; W, week.

Favorable Safety and Tolerability Profile with Zetomipzomib Treatment

Safety Population (DBTP N=23; OLE N=14)

	Double-blind Treatment Period (DBTP)		Open-label Extension (OLE)	
Adverse Events	**Placebo N=7 n (%)**	**Zetomipzomib N=16 n (%)**	**DBTP Placebo N=5 n (%)**	**DBTP Zetomipzomib N=9 n (%)**
Participants with at least 1 Treatment Emergent Adverse Event (TEAE)	7 (100.0)	16 (100.0)	5 (100.0)	9 (100.0)
Most common TEAE: Injection Site Reaction (ISR) Systemic Injection Reaction (SIR)	 4 (57.1) 1 (14.3)	 15 (93.8) 12 (75.0)	 5 (100.0) 5 (100.0)	 6 (66.7) 8 (88.9)
TEAE leading to study drug discontinuation	0 (0)	3* (18.8)	2¶ (40.0)	2# (22.2)
Grade 3 TEAE (No Grade 4 or 5 TEAEs reported)	1 (14.3)	3 (18.8)	0 (0.0)	2 (22.2)
Serious TEAE	1† (14.3)	2‡ (12.5)	0 (0.0)	0 (0.0)
Infectious TEAE	6 (85.7)	9 (56.3)	2 (40.0)	2 (22.2)
Grade ≥3 Infectious TEAE	0 (0)	1 (6.3)	0 (0.0)	0 (0.0)
Opportunistic Infections§	0 (0)	0 (0)	0 (0.0)	0 (0.0)
Death	0 (0)	0 (0)	0 (0.0)	0 (0.0)

Safety Population (N=23) includes all patients who received ≥1 dose of study treatment.
*Grade 2 unrelated AIH flare (treatment failure per protocol), Grade 2 related hives, and Grade 1 related fatigue.
†Grade 3 unrelated variceal bleeding x2, with hematemesis and atrial fibrillation.
‡Grade 3 unrelated fever (post-liver biopsy) and unrelated Grade 3 Influenza B infection.
§Opportunistic infections were evaluated by sponsor through clinical assessment of reported infections.
¶Grade 1 related dyspnea; Grade 1 related pyrexia.
#Grade 2 related injection site pruritus; Grade 1 related pyrexia.

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PORTOLA Marks First Successful Randomized Phase 2 Trial in Relapsed/Refractory AIH

- Zetomipzomib demonstrates rapid, durable, and steroid-sparing disease modifying activity in a difficult-to-treat population of patients with AIH
- Favorable safety and tolerability profile observed with zetomipzomib, consistent across multiple autoimmune studies (>300 patients)
- Positive PORTOLA results and safety data across multiple autoimmune studies support advancement of zetomipzomib into a fully powered confirmatory trial in AIH

Significant unmet needs in AIH remain

- No FDA-approved therapies exist for AIH — accepted current standard first line treatment has remained largely unchanged since adoption more than 40 years ago

Advancing novel treatment options in autoimmune hepatitis requires active dialogue and collaboration across global stakeholders — including regulators, industry, HCPs, and patients

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

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