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REMISSION FROM CUTANEOUS MANIFESTATIONS OF LUPUS WITH ENPATORAN, A FIRST-IN-CLASS ORAL SMALL MOLECULE TOLL-LIKE RECEPTOR 7/8 INHIBITOR: POOLED POST-HOC EXPLORATORY ANALYSIS FROM A RANDOMIZED PLACEBO-CONTROLLED PHASE II STUDY



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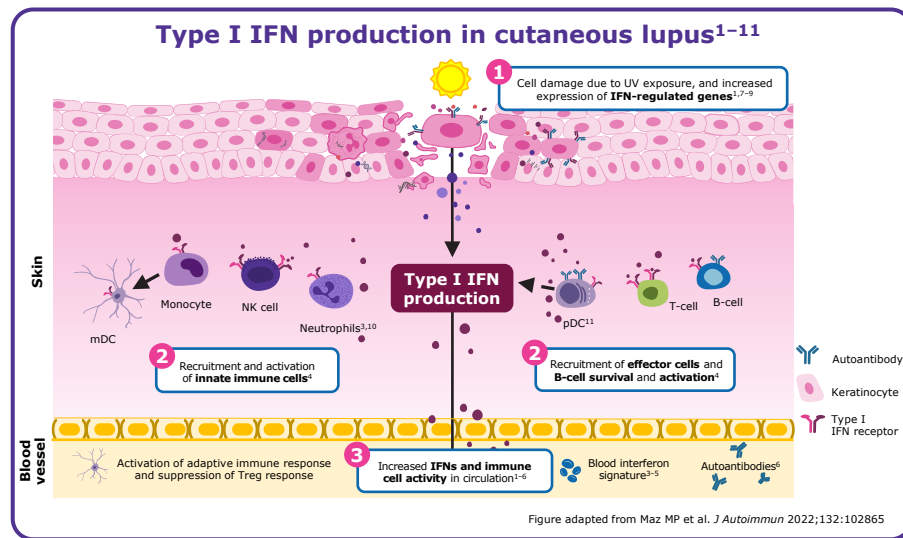
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Disclosures

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Cutaneous manifestations of lupus need treatments that target underlying pathogenesis

- **Cutaneous manifestations of lupus:**
 - Can **occur in isolation ('CLE')** or in the context of **SLE**
 - Are associated with worsening **physical and mental health and fatigue**
- There are **no approved targeted therapies** for **cutaneous disease** in lupus
- **TLR7 and 8** are key upstream drivers of the **IFN pathway and neutrophil, myeloid cell, and B-cell activation**¹²⁻¹⁴
- **Enpatoran** is a novel oral small molecule dual **inhibitor of TLR7/8**¹⁵



Cutaneous IFN activation may trigger systemic autoantibody production and inflammation^{1,4}

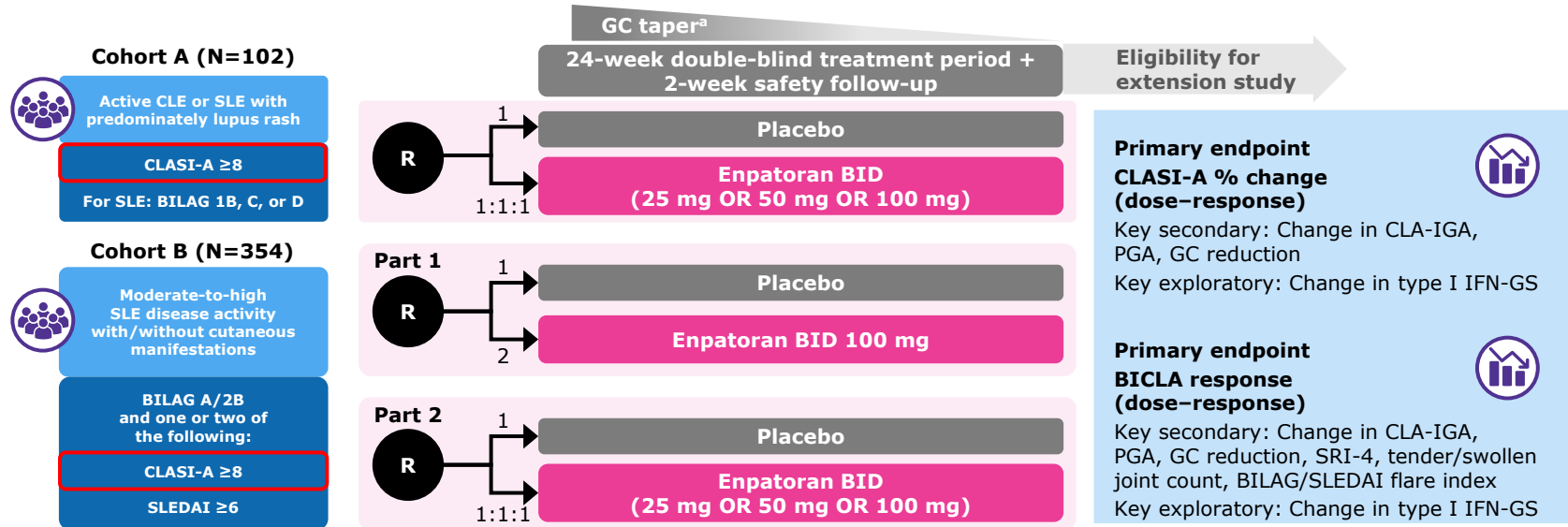
CLE, cutaneous lupus erythematosus; **IFN**, interferon; **mDC**, myeloid dendritic cell; **NK**, natural killer; **pDC**, plasmacytoid dendritic cell; **SLE**, systemic lupus erythematosus; **TLR**, toll-like receptor; **UV**, ultra-violet.

1. Maz MP, et al. *J Autoimmun* 2022;132:102865; 2. Zhou X, et al. *Scand J Immunol* 2021;93:e12933; 3. Psarras A, et al. *Nat Rev Rheumatol* 2022;18:575-590; 4. Psarras A, et al. *Nat Commun* 2020;11:6149; 5. Skopelja-Gardner S, et al. *Sci Rep* 2020;10:7908; 6. Yokogawa M, et al. *Arthritis Rheumatol* 2014;66:694-706; 7. Vazquez T, et al. *J Invest Dermatol* 2024;144:1262-72.e7; 8. Petty AJ, et al. *Curr Allergy Asthma Rep* 2020;20:12; 9. Stannard JN, Kahlenberg JM. *Curr Opin Rheumatol* 2016;28:453-459; 10. Futosi K, et al. *Int Immunopharmacol* 2013;17:638-650; 11. Fitzgerald-Bocarsly P, et al. *Cytokine Growth Factor Rev* 2008;19:3-19; 12. Bender AT, et al. *Immunohorizons* 2020;4:93-107; 13. Al-Azab M, et al. *Nat Immunol* 2024;25:969-980; 14. Wang T, et al. *Front Immunol* 2024;15:1515469; 15. Vlach J, et al. *J Pharmacol Exp Ther* 2020;376:397-409.

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WILLOW study design and pooled analysis

Phase II randomized double-blind placebo-controlled dose-finding parallel adaptive study in adults with CLE or SLE receiving SoC



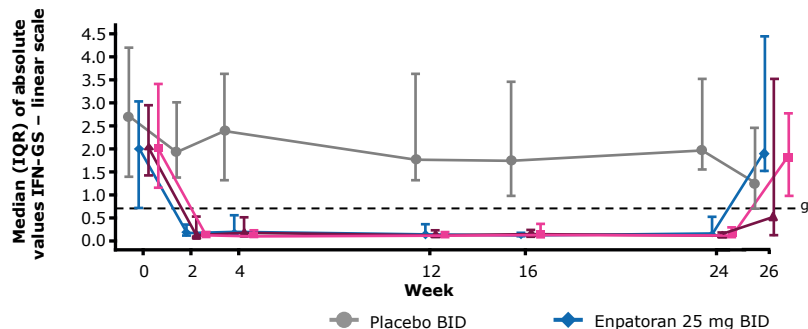
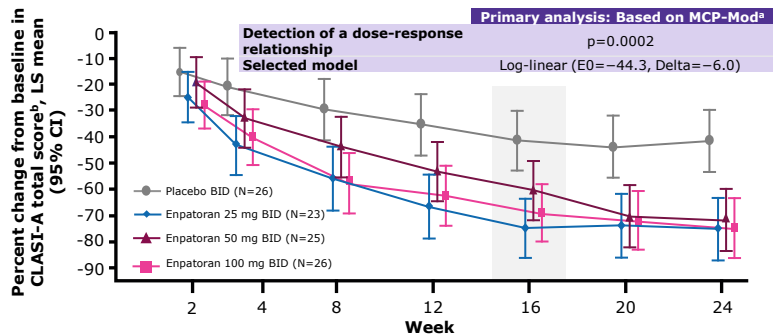
^aGC tapering is defined as a reduction of daily GC dose by Week 12 and then sustaining the dose through Week 24.

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; **BID**, twice daily; **BILAG**, British Isles Lupus Assessment Group; **CLA-IGA**, Cutaneous Lupus Activity Investigator's Global Assessment; **CLASI**, Cutaneous Lupus Erythematosus Disease Area and Severity Index; **CLASI-A**, CLASI-activity; **CLE**, cutaneous lupus erythematosus; **GC**, glucocorticoid; **IFN-GS**, interferon gene signature; **PGA**, Physician's Global Assessment; **R**, randomization; **SLE**, systemic lupus erythematosus; **SLEDAI**, Systemic Lupus Erythematosus Disease Activity Index; **SoC**, standard of care; **SRI-4**, SRI Responder Index-4.

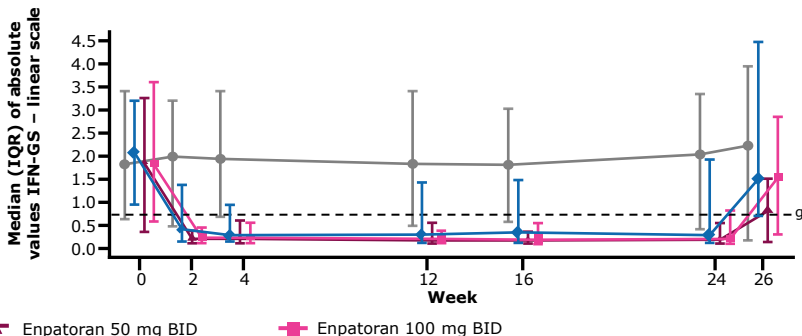
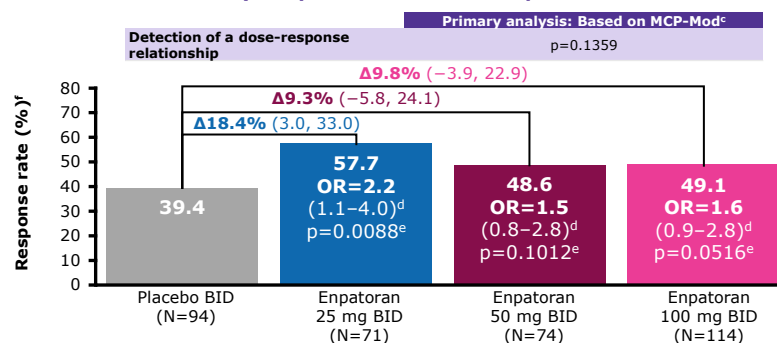
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WILLOW primary endpoint and exploratory IFN-GS results

Cohort A¹
Primary endpoint: % change in CLASI-A total score dose response at Week 16



Cohort B²
Primary endpoint: BICLA dose response at Week 24



¹MCP-Mod adjusted for CLASI-A at baseline, region and disease diagnosis (CLE only vs CLE + SLE; FAS; N=100); ²MMRM analyses (exploratory endpoint); ³MCP-Mod adjusted for BL hybrid SELENA-SLEDAI total score, region and biomarker status; ⁴95% CI using the Wald method; ⁵Nominal p-value, one-sided, vs placebo; ⁶Supplementary analysis; ⁷Dotted line represents the cut-off between participants with low IFN-GS (<0.71) and high IFN-GS (≥0.71) at baseline. **BICLA**, British Isles Lupus Assessment Group-based Composite Lupus Assessment; **BID**, twice daily; **BL**, baseline; **CI**, confidence interval; **CLASI**, Cutaneous Lupus Disease Area and Severity Index; **CLASI-A**, CLASI-Activity; **CLE**, cutaneous lupus erythematosus; **FAS**, full analysis set; **IFN-GS**, interferon gene signature; **IQR**, interquartile range; **LS**, least squares; **MCP-Mod**, Multiple Comparison Procedure-Modelling; **MMRM**, mixed model repeated measures; **OR**, odds ratio; **SLE**, systemic lupus erythematosus; **TLR**, toll-like receptor. 1. Pearson DR, et al. J Rheumatol 2025;52(Suppl 1):11; 2. Morand EF, et al. Ann Rheum Dis 2025;84(Suppl 1):316-317.

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Exploratory post-hoc pooled analysis of enpatoran effects in cutaneous manifestations of lupus

Study population

- All participants in Cohort A (FAS): Active CLE or SLE and CLASI-A ≥ 8 (N=100)
- Subgroup of participants in Cohort B: Moderate-to-high SLE disease activity and CLASI-A ≥ 8 (N=162)



Endpoints

- CLASI-A total score
- CLASI-50/70 response rates^a
- Achievement of low disease activity/remission defined as
 - CLASI-A 0–3, or
 - CLASI-A 0–1, or
 - CLA-IGA 0–1
- Change from baseline in PGA of cutaneous lupus disease activity



^aCLASI-50/70 response defined as improvement in CLASI of $\geq 50/70\%$ from baseline values.

CLA-IGA, Cutaneous Lupus Activity Investigator's Global Assessment; **CLASI**, Cutaneous Lupus Erythematosus Disease Area and Severity Index; **CLASI-A**, CLASI-Activity; **CLE**, cutaneous lupus erythematosus; **FAS**, full analysis set; **PGA**, Physician's Global Assessment; **SLE**, systemic lupus erythematosus.

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Baseline demographics and disease characteristics

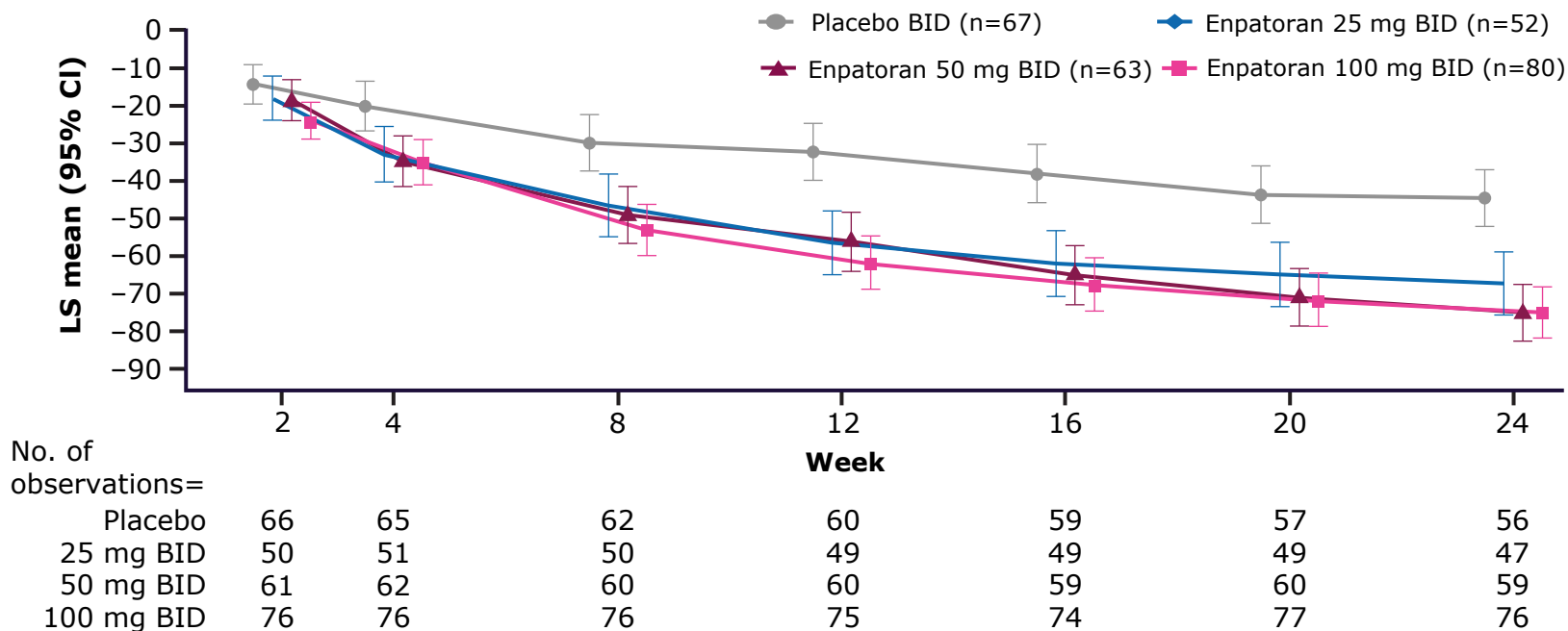
	Placebo BID (n=67)	Enpatoran 25 mg BID (n=52)	Enpatoran 50 mg BID (n=63)	Enpatoran 100 mg BID (n=80)	Total (N=262)
Demographics					
Age, years, median (range)	45 (23–68)	41 (19–66)	40 (18–74)	44 (18–69)	43 (18–74)
Sex, female, n (%)	60 (89.6)	45 (86.5)	54 (85.7)	69 (86.3)	228 (87.0)
Disease characteristics					
Diagnosis, n (%)					
SLE	53 (79.1)	38 (73.1)	48 (76.2)	65 (81.3)	204 (77.9)
CLE only	14 (20.9)	14 (26.9)	15 (23.8)	15 (18.8)	58 (22.1)
CLASI-A total score, mean (SD)	12 (4.9)	13 (6.3)	14 (7.0)	13 (5.7)	13 (6.0)
CLASI-A severity (total score), n (%)					
Mild (0–9)	23 (34.3)	20 (38.5)	17 (27.0)	27 (33.8)	87 (33.2)
Moderate (10–20)	37 (55.2)	26 (50.0)	39 (61.9)	43 (53.8)	145 (55.3)
Severe (21–70)	7 (10.4)	6 (11.5)	7 (11.1)	10 (12.5)	30 (11.5)
CLA-IGA 0 or 1, n (%)	1 (1.9)	0	0	0	0
PGA CLE disease activity score, mean (SD)	57.9 (16.1)	58.7 (15.6)	56.6 (16.7)	58.8 (17.6)	-
SELENA-SLEDAI mucocutaneous score ≥1 with manifestations in other organ systems, n (%)	40 (97.6)	28 (96.6)	37 (97.4)	51 (94.4)	156 (96.3)
Background therapy					
Immunosuppressants ^a , n (%)	30 (44.8)	27 (51.9)	32 (50.8)	41 (51.3)	130 (49.6)
Antimalarials, n (%)	53 (79.1)	38 (73.1)	46 (73.0)	66 (82.5)	203 (77.5)
Systemic GC, n (%)	48 (71.6)	38 (73.1)	50 (79.4)	58 (72.5)	194 (74.0)
Topical GC, n (%)	3 (4.5)	2 (3.8)	2 (3.2)	1 (1.3)	8 (3.1)

^aExcluding antimalarials.

BID, twice daily; **CLA-IGA**, Cutaneous Lupus Activity Investigator's Global Assessment; **CLASI-A**, Cutaneous Lupus Disease Area and Severity Index-Activity; **CLE**, cutaneous lupus erythematosus; **GC**, glucocorticoids; **PGA**, Physician Global Assessment; **SD**, standard deviation; **SELENA-SLEDAI**, Safety of Estrogens in Systemic Lupus Erythematosus National Assessment- Systemic Lupus Erythematosus Disease Activity Index; **SLE**, systemic lupus erythematosus.

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Change from baseline in CLASI-A total score

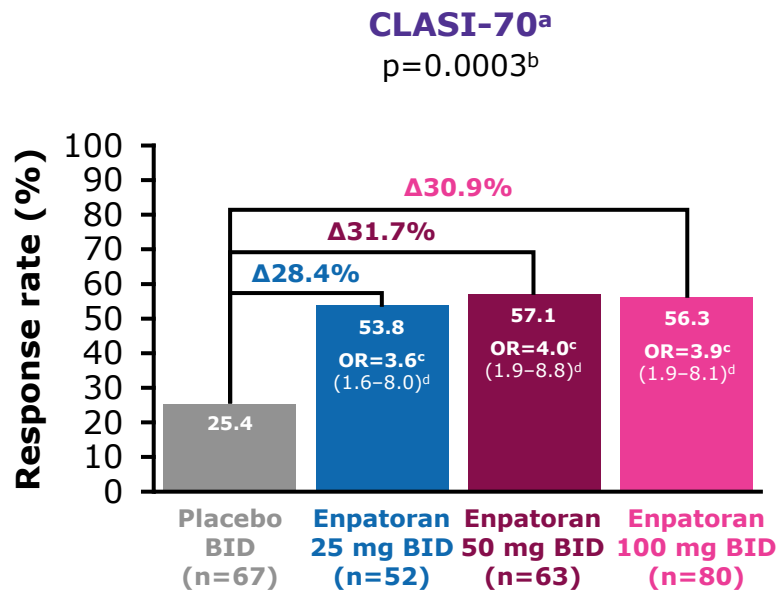
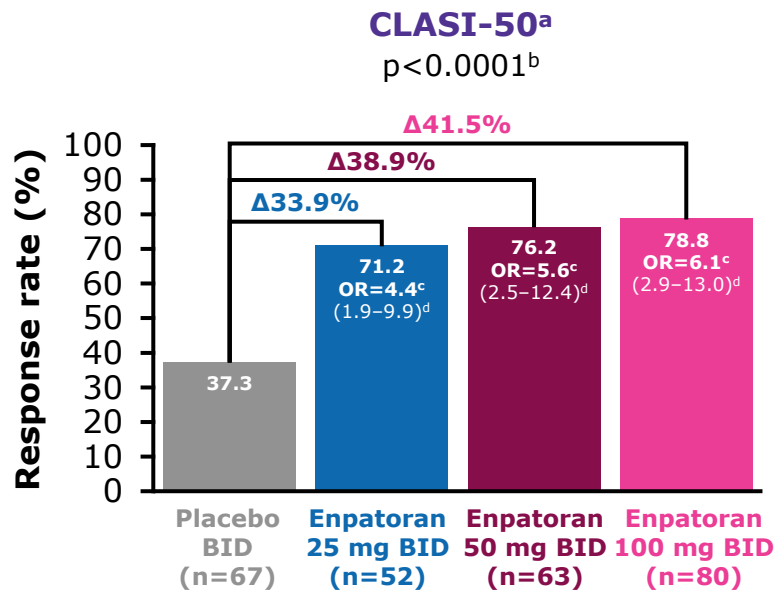


Enpatoran improved CLASI-A total score vs placebo from Week 4

Post-hoc exploratory pooled analysis (participants from Cohorts A and B with CLASI-A ≥ 8 at baseline, N=262)

BID, twice daily; CLASI-A, Cutaneous Lupus Disease Area and Severity Index-Activity; LS, least squares.
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CLASI-50/70 response rates at Week 24

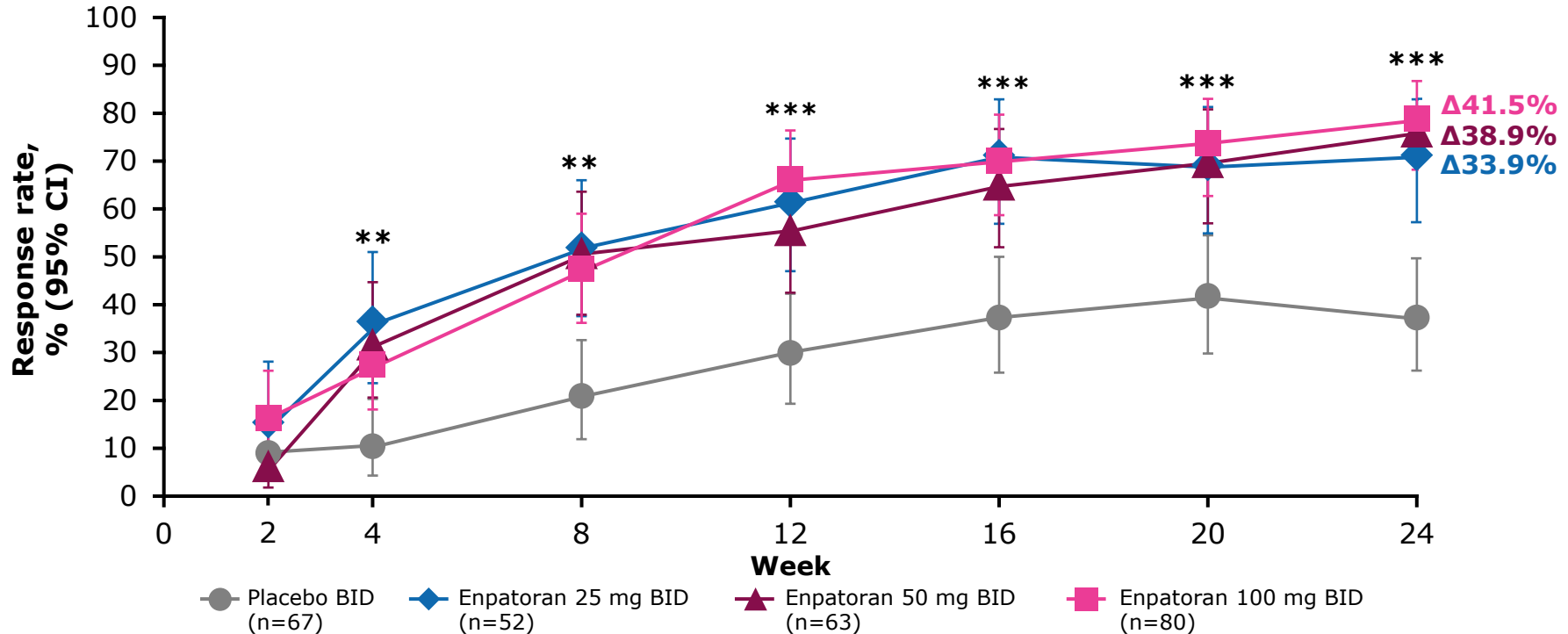


Post-hoc exploratory pooled analysis (participants from Cohorts A and B with CLASI-A ≥8 at baseline, N=262)

^aCLASI-50/70 response defined as ≥50%/70% improvement from baseline in CLASI-A total score; ^bNominal p-value for overall treatment effect of enpatoran versus placebo based on Likelihood Ratio Chi-square test; ^cBased on a logistic model adjusted for treatment, region, baseline CLASI-A and disease subtype; ^d95% CI calculated using the Clopper-Pearson exact method.

BID, twice daily; **CI**, confidence interval; **CLASI**, Cutaneous Lupus Disease Area and Severity Index; **CLASI-A**, CLASI-Activity; **OR**, odds ratio.
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CLASI-50^a response rates over time



Post-hoc exploratory pooled analysis (participants from Cohorts A and B with CLASI-A ≥ 8 at baseline, N=262)

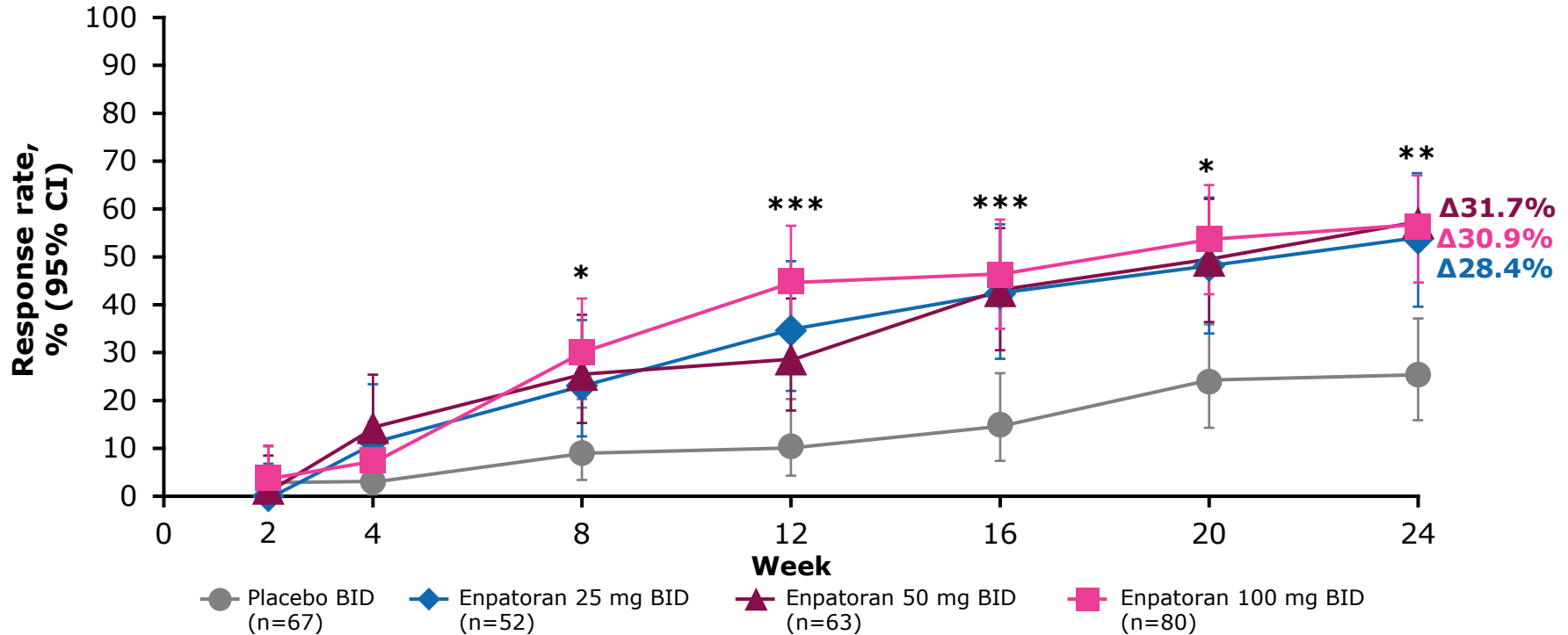
p ≤ 0.001 ; *p ≤ 0.0001 Nominal p-value for overall treatment effect of enpatoran versus placebo based on Likelihood Ratio Chi-square test.

^aCLASI-50 response defined as $\geq 50\%$ improvement from baseline in CLASI-A total score. Logistic model analyses adjusted for treatment, region, baseline CLASI-A and disease subtype (SCLE/DLE, ACLE without SCLE/DLE, Other).

ACLE, acute cutaneous lupus erythematosus; BID, twice daily; CI, confidence interval; CLASI, Cutaneous Lupus Disease Area and Severity Index; CLASI-A, CLASI-Activity; DLE, discoid lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus.

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CLASI-70^a response rates over time



Post-hoc exploratory pooled analysis (participants from Cohorts A and B with CLASI-A ≥ 8 at baseline, N=262)

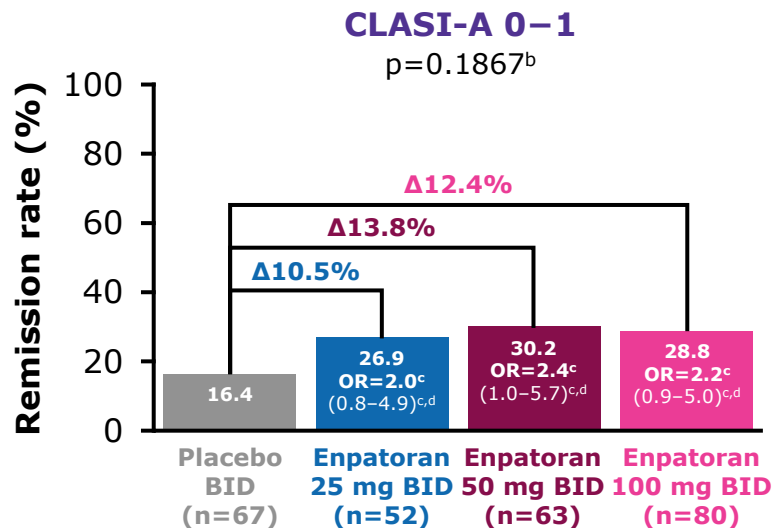
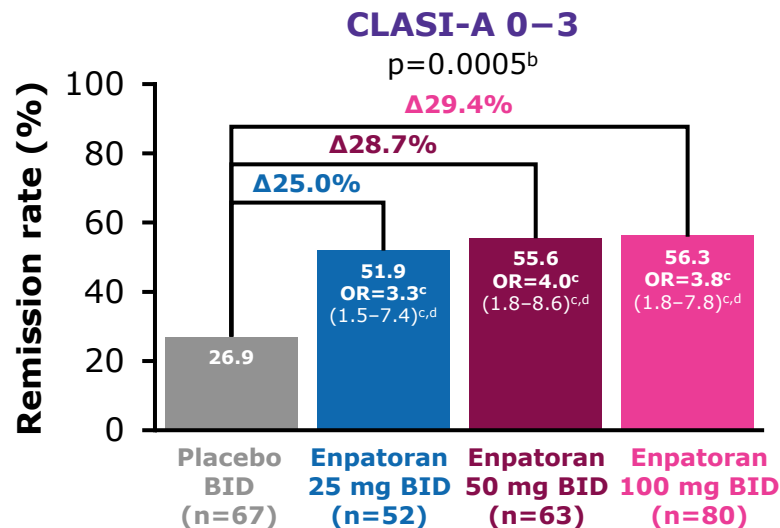
*p<0.05; **p \leq 0.001; ***p \leq 0.0001 Nominal p-value for overall treatment effect of enpatoran versus placebo based on Likelihood Ratio Chi-square test.

^aCLASI-70 response defined as $\geq 70\%$ improvement from baseline in CLASI-A total score. Logistic model analyses adjusted for treatment, region, baseline CLASI-A and disease subtype (SCLE/DLE, ACLE without SCLE/DLE, Other).

ACLE, acute cutaneous lupus erythematosus; BID, twice daily; CI, confidence interval; CLASI, Cutaneous Lupus Disease Area and Severity Index; CLASI-A, CLASI-Activity; DLE, discoid lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus.

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Low disease activity (CLASI-A 0–3)^a or remission (CLASI-A 0–1)^a at Week 24



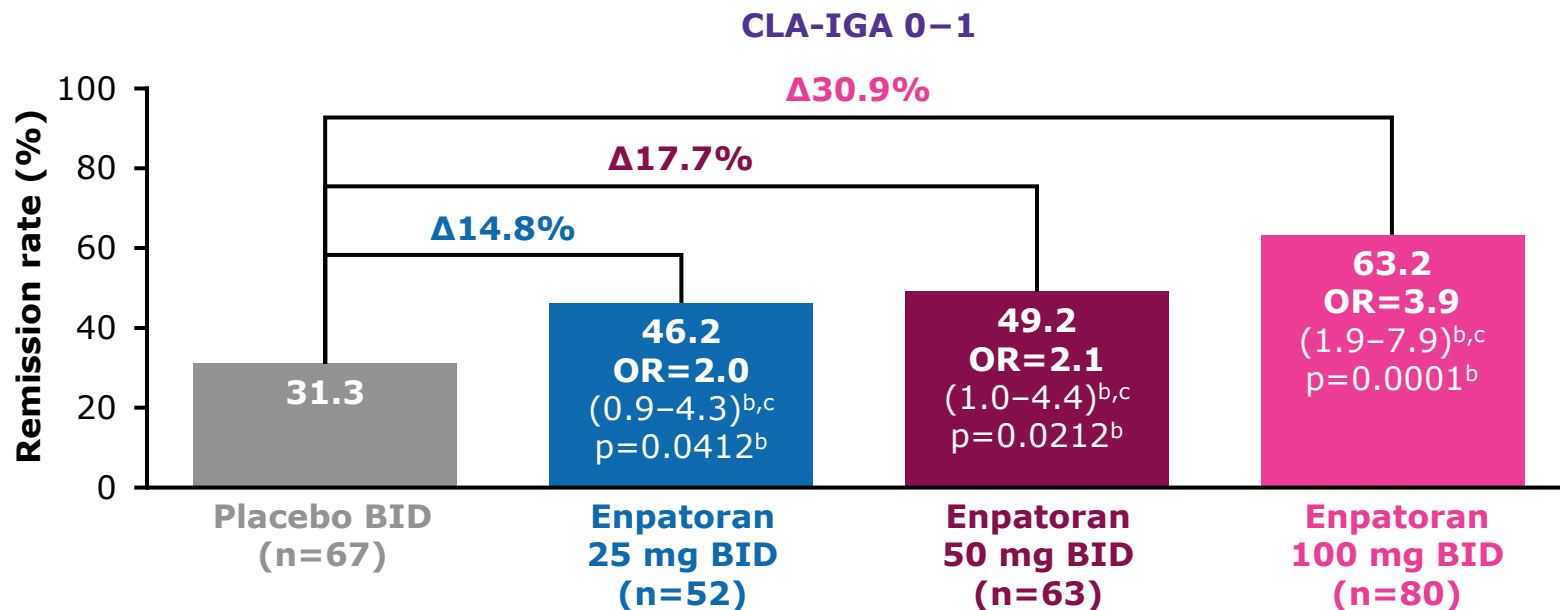
Post-hoc exploratory pooled analysis (participants from Cohorts A and B with CLASI-A ≥ 8 at baseline, N=262); ^aExploratory definitions

^bNominal p-value for overall treatment effect of enpatoran versus placebo based on Likelihood Ratio Chi-square test; ^cBased on a logistic model adjusted for treatment, region, baseline CLASI-A and disease subtype; ^d95% CI calculated using the Clopper-Pearson exact method.

BID, twice daily; **CLASI-A**, Cutaneous Lupus Disease Area and Severity Index-Activity; **OR**, odds ratio.

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Remission (CLA-IGA 0–1)^a at Week 24



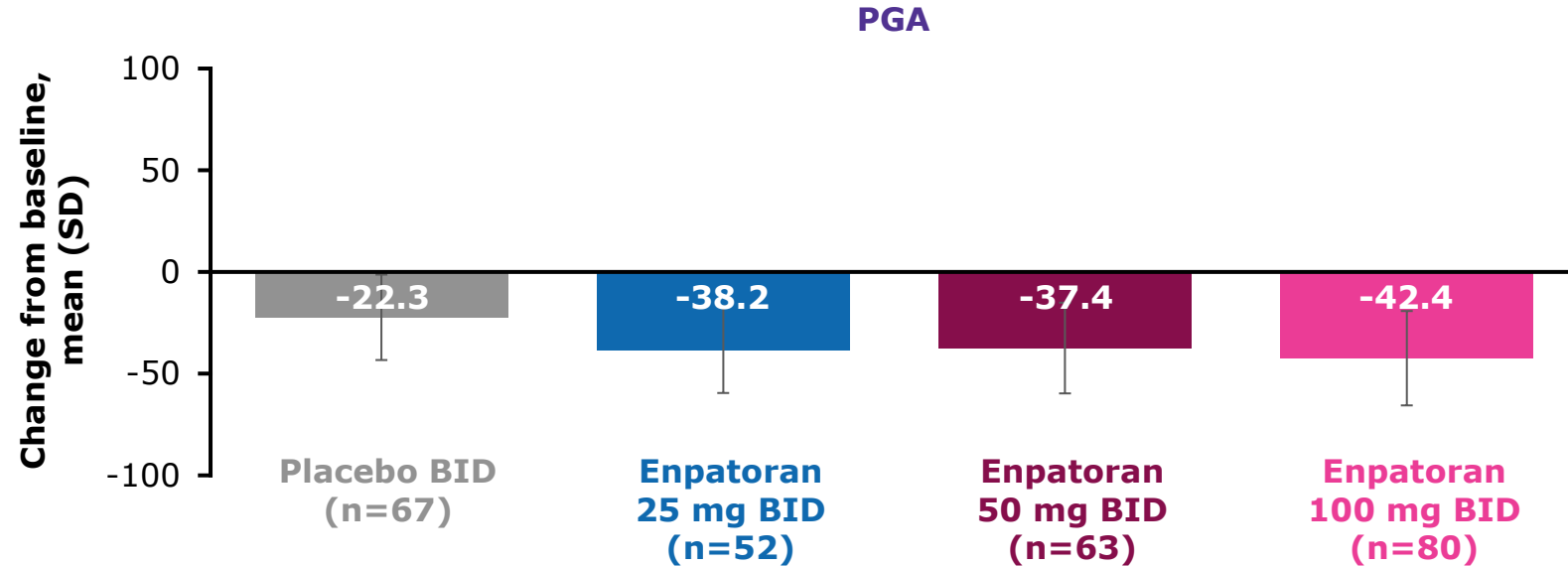
Post-hoc exploratory pooled analysis (participants from Cohorts A and B with CLASI-A ≥ 8 at baseline, N=262); ^aExploratory definition

^bBased on a logistic model with treatment group, region and cohort as independent variables. There was no adjustment for multiplicity and p-values are nominally significant $p < 0.025$; ^c95% CI calculated using the Wald method.

BID, twice daily; **CI**, confidence interval; **CLA-IGA**, Cutaneous Lupus Activity investigator's Global Assessment; **CLASI-A**, Cutaneous Lupus Disease Area and Severity Index-Activity; **OR**, odds ratio.

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Change in cutaneous lupus disease activity PGA at Week 24



Post-hoc exploratory pooled analysis (participants from Cohorts A and B with CLASI-A ≥ 8 at baseline, N=262)

BID, twice daily; PGA, Physician Global Assessment; SD, standard deviation.

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Conclusions

Enpatoran improved skin-related outcomes for participants with cutaneous lupus, regardless of diagnosis of CLE or SLE

CLASI-A total score, CLASI-50 and CLASI-70 response rates were significantly increased at Week 24 versus placebo

- Treatment effect observed as early as Week 4

Low cutaneous disease activity/remission rates were improved versus placebo

- 51.9% to 56.3% of enpatoran-treated participants attained CLASI-A ≤ 3
- 46.2% to 63.2% of enpatoran-treated participants attained CLA-IGA ≤ 1

Phase 3 trials of enpatoran for people living with lupus are warranted

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