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# RANDOMISED, PLACEBO-CONTROLLED PHASE II STUDY OF ORAL ENPATORAN, A FIRST-IN-CLASS TOLL-LIKE RECEPTOR 7/8 INHIBITOR, IN SYSTEMIC LUPUS ERYTHEMATOSUS



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# Disclosures

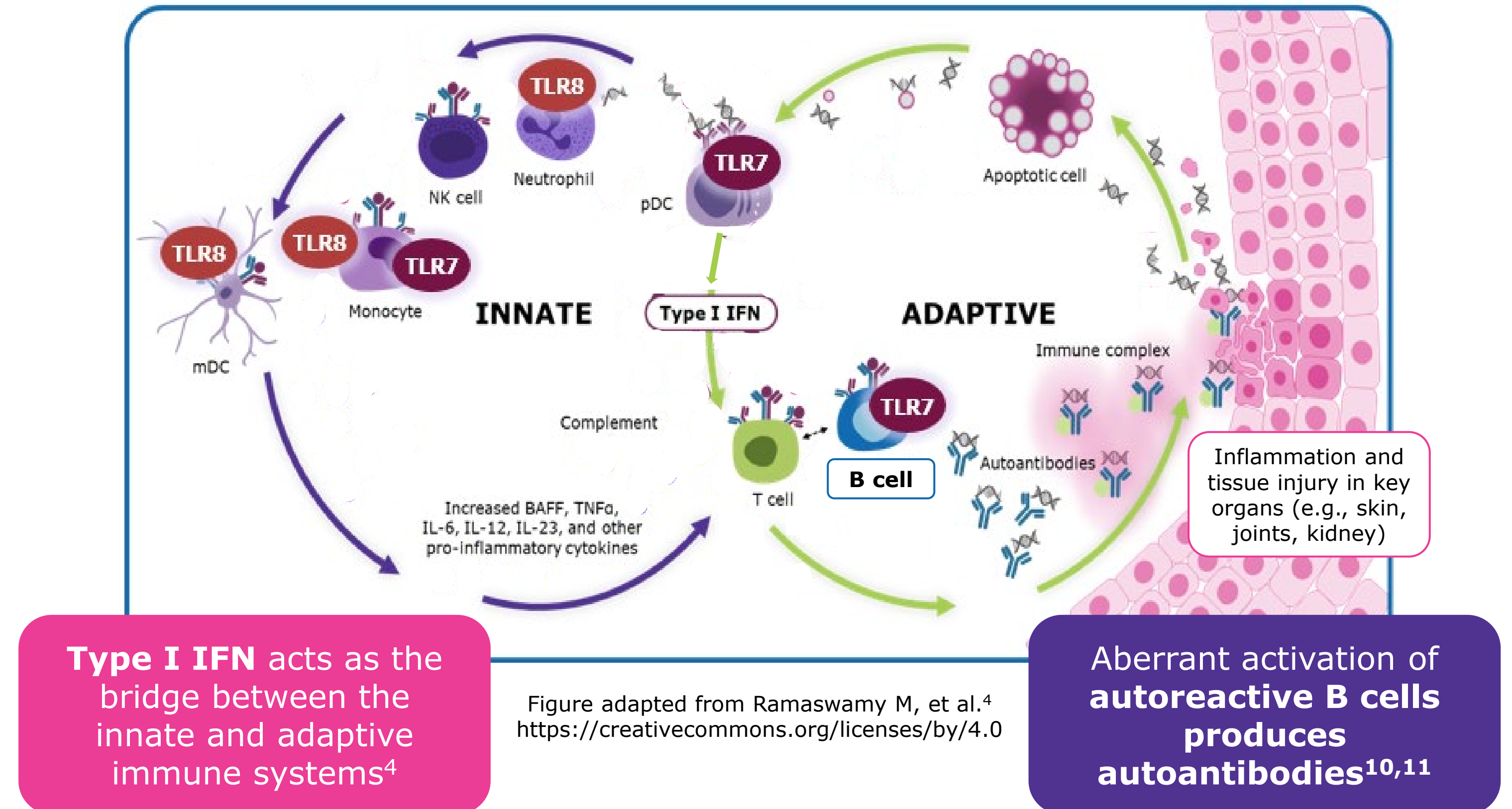
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# Targeting lupus pathophysiology with TLR7/8 inhibition

- **TLR7 and 8** are key upstream drivers of the **IFN pathway** and **B cell activation**<sup>1-4</sup>
- **Enpatoran** is a potential **small-molecule, oral therapy** that **modulates innate and adaptive immunity** through **reversible, dual inhibition of TLR7/8**<sup>5</sup>
- Early **clinical trials** demonstrated that **enpatoran** was **well tolerated**<sup>6-9</sup>



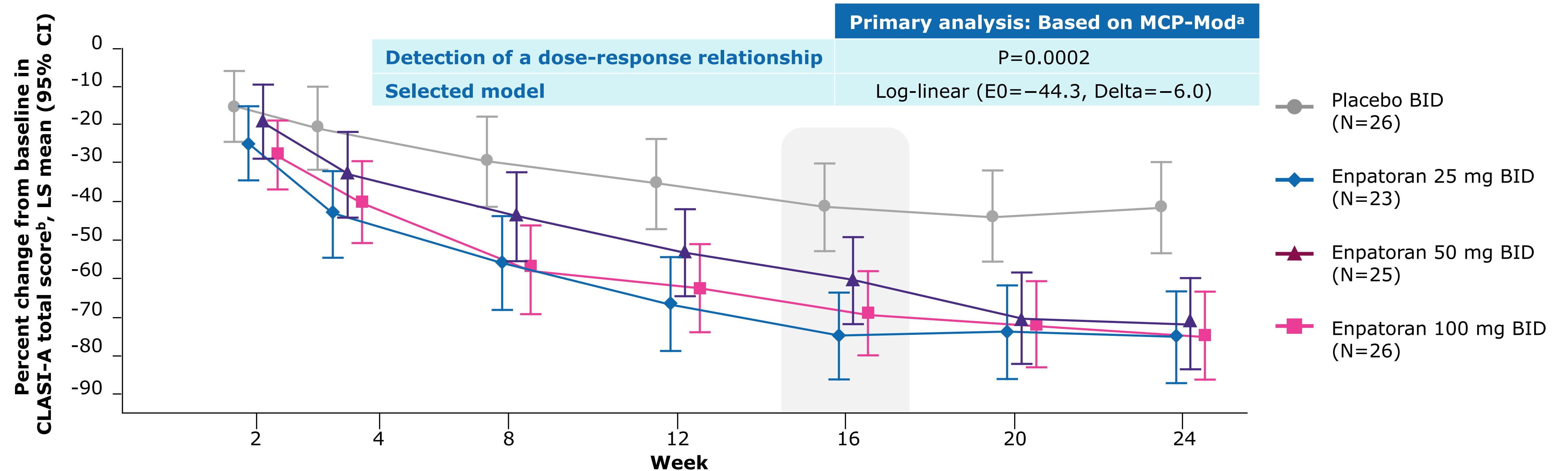
**BAFF**, B-cell activating factor; **IFN**, interferon; **IL**, interleukin; **mDC**, myeloid dendritic cell; **NK**, natural killer; **pDC**, plasmacytoid dendritic cell; **TLR**, toll-like receptor; **TNF**, tumor necrosis factor.

1. Brown GJ, et al. *Nature* 2022;605:349–56; 2. Aluri J, et al. *Blood* 2021;137:2450–62; 3. Tanaka Y, et al. *RMD Open* 2024;10:e004701; 4. Ramaswamy M, et al. *Int J Mol Sci* 2021;22:11286; 5. Vlach J, et al. *J Pharmacol Exp Ther* 2020;376:397–409; 6. Port A, et al. *Pharmacol Res Perspect* 2021;9:e00842; 7. Klopp-Schulze L, et al. *Clin Pharmacol Ther* 2024;115:1346–57; 8. McKinnon JE, et al. *Clin Transl Sci* 2023;16:2640–53; 9. Witte T, et al. *ACR* 2024. Abstract 1553; 10. Pan L, et al. *World J Pediatr* 2020;16:19–30; 11. Liu T, et al. *Front Immunol* 2020;11:1057.

**Enpatoran is an investigational product and has not been proven to be safe and effective in any country**



# Cohort A: Primary endpoint



N obs=	2	4	8	12	16	20	24
Placebo BID	25	24	23	23	23	23	20
25 mg BID	22	23	23	22	22	22	22
50 mg BID	23	24	24	23	24	23	23
100 mg BID	25	25	25	24	25	25	24

**Significant dose response for enpatoran in reducing CLASI-A from baseline to Week 16**

<sup>a</sup>MCP-Mod adjusted for CLASI-A at baseline, region and disease diagnosis (CLE only vs CLE + SLE; FAS; N=100); <sup>b</sup>MMRM analyses (exploratory endpoint).  
**BID**, twice daily; **CI**, confidence interval; **CLASI-A**, Cutaneous Lupus Erythematosus Disease Area and Severity Index – Activity; **FAS**, full analysis set; **LS**, least squares;  
**MCP-Mod**, multiple comparison procedures-modelling; **MMRM**, mixed model repeated measures; **N obs**, number of observations.

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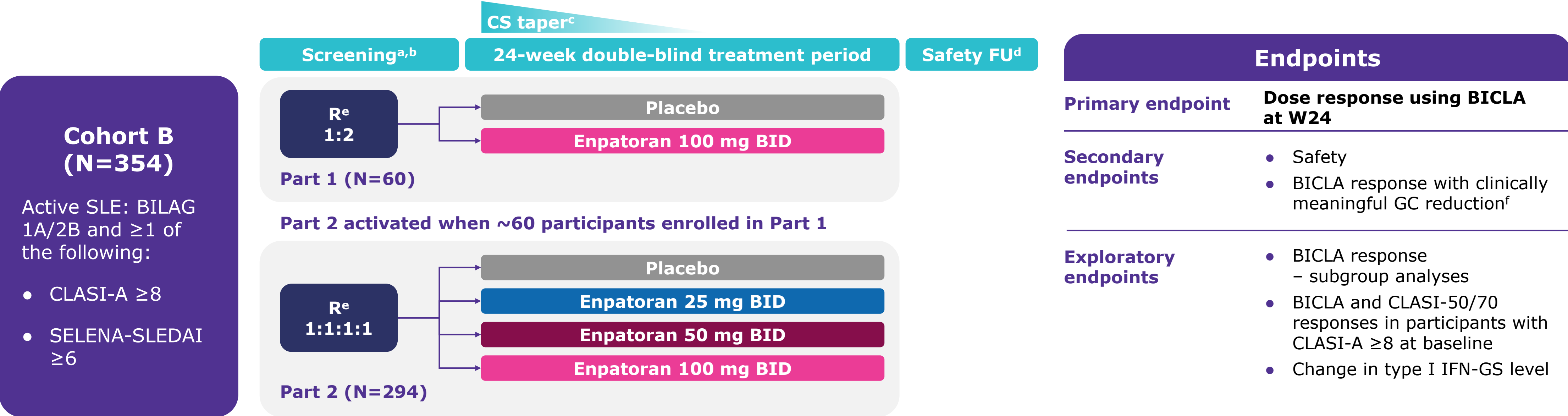


# Cohort B: Study design

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

### Primary objective

To evaluate the dose-response relationship of enpatoran in reducing disease activity based on BICLA response



NCT05162586. <sup>a</sup>No CS changes during screening; <sup>b</sup>Screening took place from Week -5 to -7 before randomisation; <sup>c</sup>From week 2; CS tapering is defined as a reduction of daily CS dose by Week 12 and then sustaining the dose through Week 24; <sup>d</sup>Up to Week 26; <sup>e</sup>Randomisation stratified by 1) region: Asia, North America and Western Europe, or Central/South America and rest of the world; 2) biomarker status at screening: IFN-GS low or IFN-GS high; 3) hybrid SELENA-SLEDAI score at screening: ≥10 or <10; <sup>f</sup>Reduction of daily prednisone-equivalent dose from ≥10 mg at Day 1 to ≤5 mg by the Week 12 visit and sustained through Week 24.

**BICLA**, British Isles Lupus Assessment Group-based Composite Lupus Assessment; **BID**, twice daily; **BILAG**, British Isles Lupus Assessment Group; **CLASI-A**, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity; **CLE**, cutaneous lupus erythematosus; **CS**, corticosteroid; **FU**, follow-up; **GC**, glucocorticoid; **IFN-GS**, interferon gene signature; **R**, randomization; **SELENA-SLEDAI**, Safety of Estrogens in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; **SLE**, systemic lupus erythematosus; **SoC**, standard of care; **SRI**, Systemic Lupus Erythematosus Responder Index.

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# Study population

## Inclusion criteria

- Adults aged  $\geq 18$  to  $\leq 75$  years
- Diagnosis of SLE (per SLICC and/or  $\geq 4$  ACR and/or EULAR/ACR 2019 criteria)
- Moderate-to-high systemic disease activity with BILAG A/2B and:
  - CLASI-A  $\geq 8$  and/or
  - SELENA-SLEDAI  $\geq 6$
- Receiving stable dose of  $\geq 1$ :
  - Immunomodulator/immunosuppressant  $\geq 8$  weeks prior to screening period
  - Oral CS  $\geq 2$  weeks prior to screening
  - Topical CS  $\geq 2$  weeks prior to screening

## Exclusion criteria

- Autoimmune or rheumatic disease other than SLE or CLE
- Dermatological diseases other than cutaneous manifestations of SLE or CLE
- Uncontrolled medical conditions including CV events, active lupus nephritis or active neurological disorder
- History of uncontrolled seizures or neurological disorder
- Ongoing or active clinically significant viral, bacterial, or fungal infection
- History of, or positive for HIV, HCV or HBV
- History of malignancy

**ACR**, American College of Rheumatology; **BILAG**, British Isles Lupus Assessment Group; **CLASI-A**, Cutaneous Lupus Erythematosus Area and Severity Index – Activity; **CLE**, cutaneous lupus erythematosus; **CS**, corticosteroid; **CV**, cardiovascular; **EULAR**, European League Against Rheumatism; **HBV**, hepatitis B virus; **HCV**, hepatitis C virus; **HIV**, human immunodeficiency virus; **SELENA-SLEDAI**, Safety of Estrogens in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; **SLE**, systemic lupus erythematosus; **SLICC**, Systemic Lupus International Collaborating Clinics.

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## Baseline characteristics

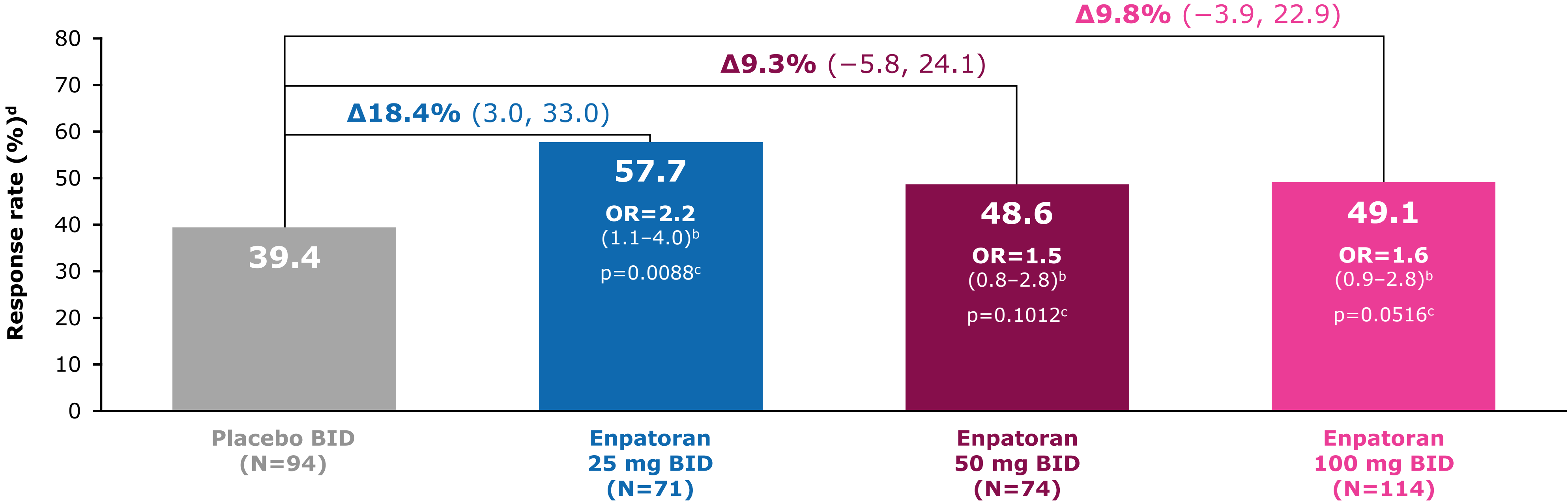
	Placebo BID (N=94)	Enpatoran 25 mg BID (N=71)	Enpatoran 50 mg BID (N=74)	Enpatoran 100 mg BID (N=114)
<b>Demographics</b>				
Age, years (mean ± SD)	42 ± 12.3	42 ± 12.4	39 ± 12.3	44 ± 12.2
Sex, female, n (%)	87 (92.6)	69 (97.2)	69 (93.2)	110 (96.5)
<b>Disease characteristics, n (%)</b>				
Hybrid SLEDAI mucocutaneous score >0 with manifestations in other organ systems	90 (95.7)	70 (98.6)	70 (94.6)	110 (96.5)
Hybrid SLEDAI musculoskeletal score >0	89 (94.7)	64 (90.1)	69 (93.2)	104 (91.2)
<b>Biomarker status, n (%)</b>				
IFN-GS high and/or positive RNA autoantibodies	76 (80.9)	59 (83.1)	57 (77.0)	91 (79.8)
IFN-GS low and negative RNA autoantibodies	18 (19.1)	12 (16.9)	17 (23.0)	23 (20.2)
<b>Hybrid SLEDAI total score at baseline (mean ± SD)</b>				
<10, n (%)	33 (35.1)	20 (28.2)	23 (31.1)	34 (29.8)
≥10, n (%)	61 (64.9)	51 (71.8)	51 (68.9)	80 (70.2)
<b>CS use, n (%)</b>				
CS use ≥10 mg	51 (54.3)	34 (47.9)	36 (48.6)	59 (51.8)

**BID**, twice daily; **CS**, corticosteroid; **IFN-GS**, interferon gene signature; **RNA**, ribonucleic acid; **SD**, standard deviation; **SLEDAI**, Systemic Lupus Erythematosus Disease Activity Index; **SoC**, Standard of Care.  
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# Primary endpoint: BICLA dose response at Week 24

Detection of a dose-response relationship Primary analysis: Based on MCP-Mod<sup>a</sup>  
p=0.1359



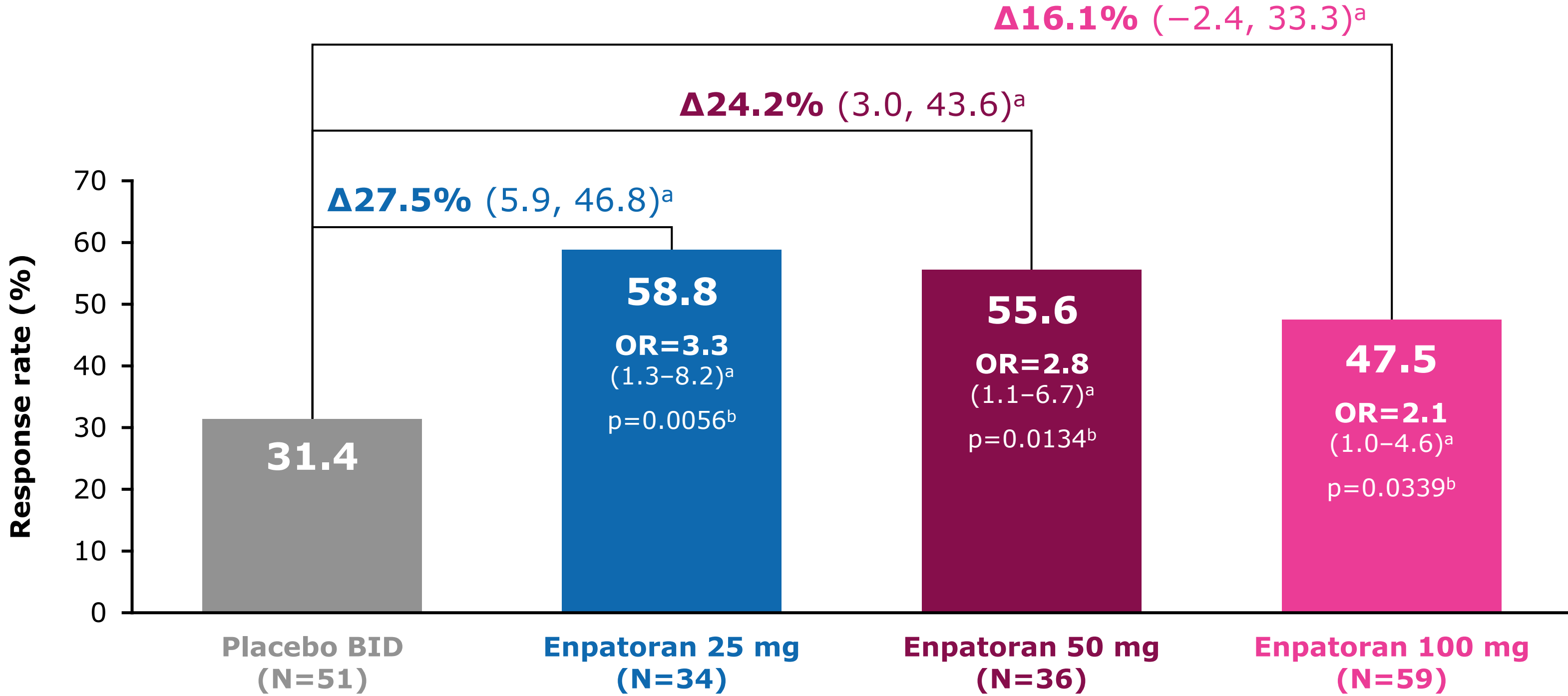
**Enpatoran was associated with higher BICLA response rates vs placebo, although no statistically significant dose-response relationship was identified**

Full analysis set, N=353.

<sup>a</sup>MCP-Mod adjusted for BL hybrid SELENA-SLEDAI total score, region and biomarker status; <sup>b</sup>95% CI using the Wald method; <sup>c</sup>Nominal p-value, one-sided, vs placebo; <sup>d</sup>Supplementary analysis.  
**BICLA**, British Isles Lupus Assessment Group-based Composite Lupus Assessment; **BID**, twice daily; **BL**, baseline; **MCP-Mod**, multiple comparison procedure – modelling; **OR**, odds ratio; **SLE**, systemic lupus erythematosus.  
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# Secondary endpoint: BICLA response + clinically meaningful GC reduction



Reduction of prednisone-equivalent dose from  $\geq 10$  mg/day at Day 1 to  $\leq 5$  mg/day by Week 12 sustained through Week 24

Higher rates of BICLA response + clinically meaningful GC reduction in all enpatoran treatment groups vs placebo at Week 24

Secondary endpoint (participants with GC dose  $\geq 10$ mg/day at BL, N=180).

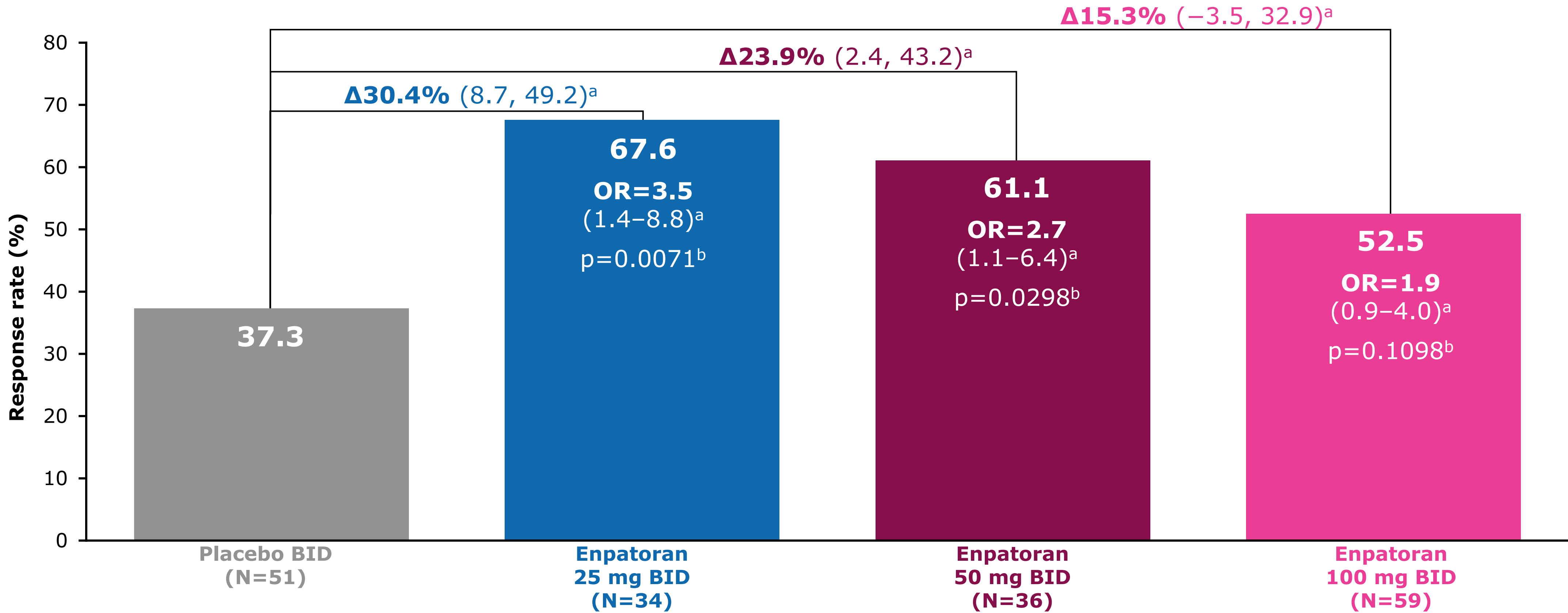
<sup>a</sup>95% confidence interval; <sup>b</sup>Nominal p-value, one-sided, vs placebo.

**BICLA**, British Isles Lupus Assessment Group-based Composite Lupus Assessment; **BID**, twice daily; **BL**, baseline; **GC**, glucocorticoid; **OR**, odds ratio.

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# Exploratory endpoint: BICLA response in participants receiving GC ≥10 mg/day at baseline



**Treatment effect of enpatoran for BICLA response rate at Week 24 demonstrated in participants receiving a high GC dose (≥10 mg/day) at baseline**

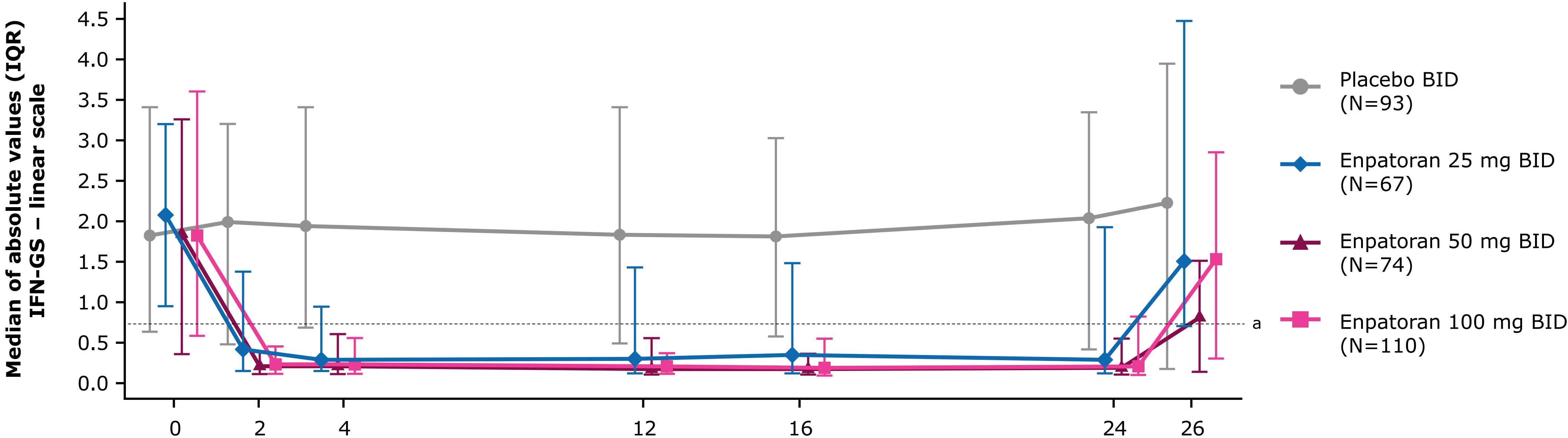
**Exploratory endpoint**

Results may be based on a limited sample size, which can affect the reliability and validity of the findings. Caution should be exercised when interpreting these results, as low numbers may lead to skewed or misleading conclusions. <sup>a</sup>95% confidence interval; <sup>b</sup>nominal p-value for treatment effect.

**BID**, twice daily; **BICLA**, British Isles Lupus Assessment Group-based Composite Lupus Assessment; **GC**, glucocorticoid; **OR**, odds ratio; **SoC**, standard of care.  
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# Exploratory endpoint: Suppression of IFN-GS



	0	2	4	12	16	24	26
<b>N obs=</b>							
<b>Placebo BID</b>	93	93	92	87	81	73	10
<b>25 mg BID</b>	67	66	67	66	66	59	6
<b>50 mg BID</b>	74	73	71	71	66	64	2
<b>100 mg BID</b>	110	106	107	104	104	101	16

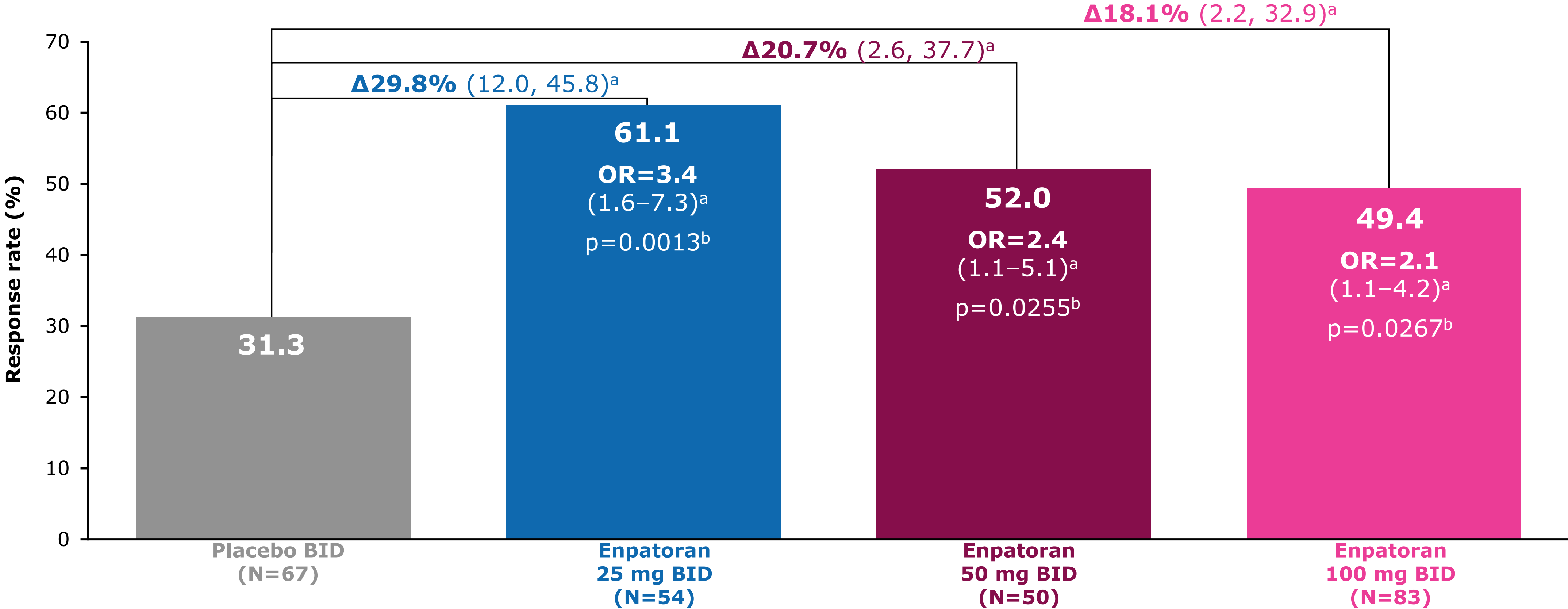
**Compared with placebo, type I IFN-GS was reduced for all enpatoran doses as early as Week 2 and maintained through Week 24**

**Exploratory endpoint (PD analysis set, N=344).**

<sup>a</sup>Dotted line represents the cut-off between participants with low IFN-GS (<0.71) and high IFN-GS (≥0.71) at baseline.  
**BID**, twice daily; **IFN**, interferon; **IFN-GS**, IFN gene signature; **IQR**, interquartile range; **PD**, pharmacodynamics; **N obs**, number of observations.  
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# Exploratory endpoint: BICLA response in participants with high IFN-GS at baseline



**Improved BICLA response rate across all enpatoran dose groups vs placebo at Week 24**

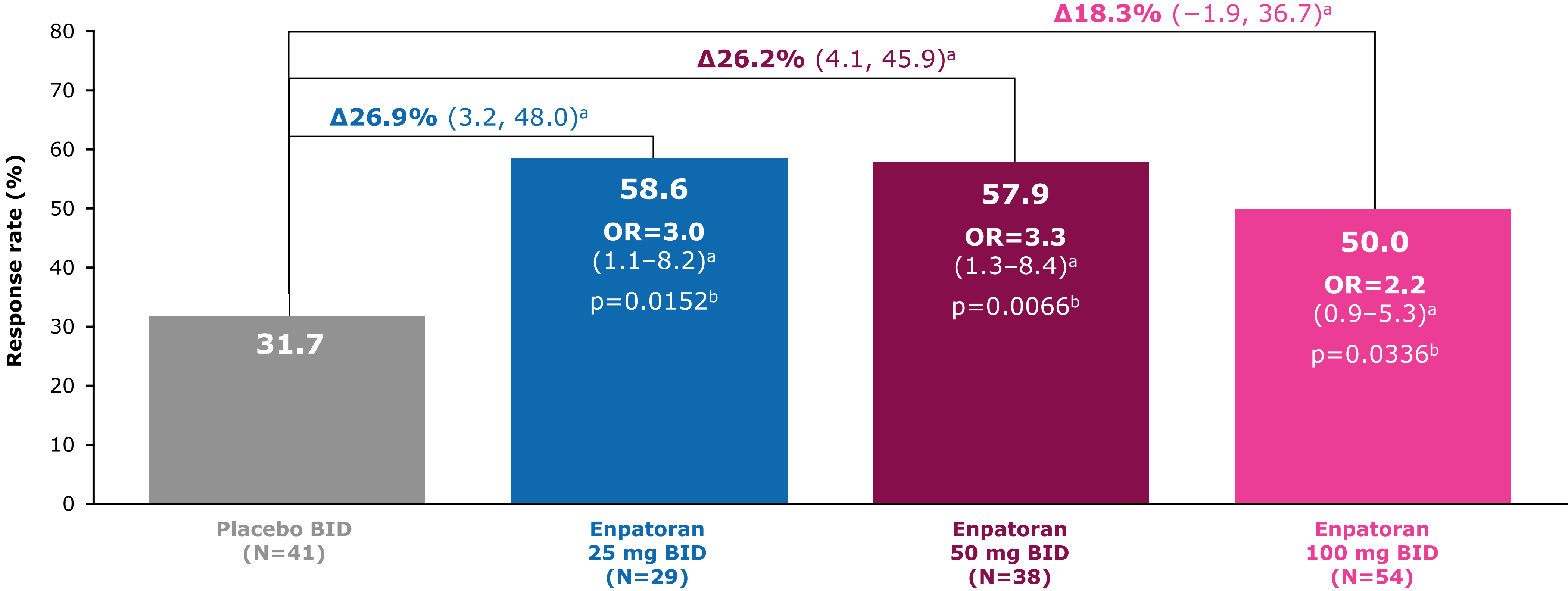
**Exploratory endpoint**

Results may be based on a limited sample size, which can affect the reliability and validity of the findings. Caution should be exercised when interpreting these results, as low numbers may lead to skewed or misleading conclusions. <sup>a</sup>95% confidence interval; <sup>b</sup>nominal p-value for treatment effect.

**BID**, twice daily; **BICLA**, British Isles Lupus Assessment Group-based Composite Lupus Assessment; **IFN-GS**, interferon gene signature; **OR**, odds ratio; **SoC**, standard of care.  
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# Exploratory endpoint: BICLA response in participants with active cutaneous manifestations (CLASI-A ≥8) at baseline



**Improved BICLA response rates with all doses of enpatoran vs placebo at Week 24**

Post-hoc analysis (participants with CLASI-A ≥8 at baseline, N=162).

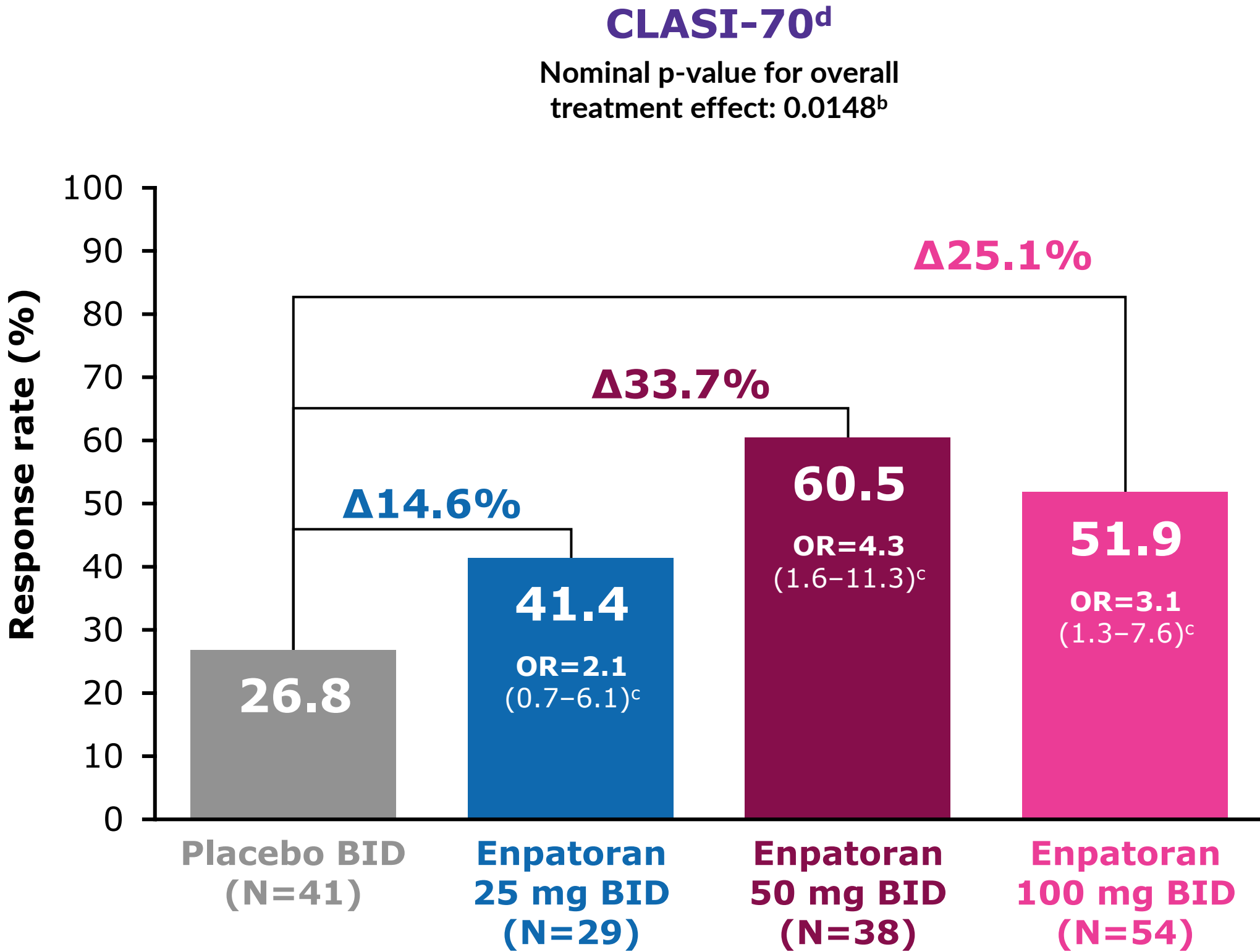
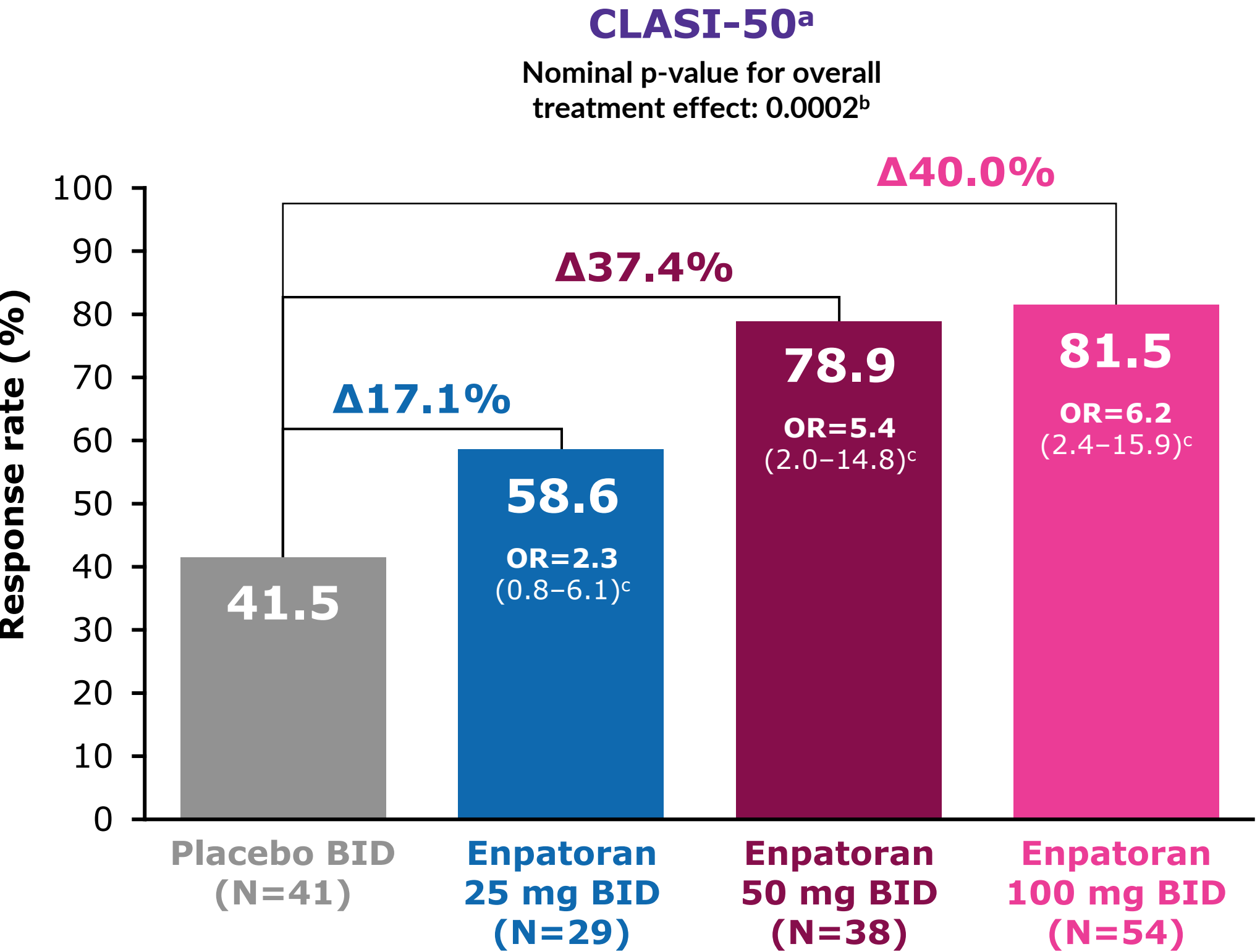
<sup>a</sup>95% confidence interval; <sup>b</sup>Nominal p-value, one sided.

**BICLA**, British Isles Lupus Assessment Group-based Composite Lupus Assessment; **BID**, twice daily; **CLASI-A**, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity.

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# Exploratory endpoints: CLASI-50 and CLASI-70 response in participants with active cutaneous manifestations (CLASI-A ≥8) at baseline



**High CLASI-50 and CLASI-70 response rates were reported at Week 24 for participants receiving enpatoran**

**Exploratory endpoint (participants with CLASI-A ≥8 at baseline, N=162).**

<sup>a</sup>CLASI-50 response was defined as a decrease in CLASI of ≥50% from baseline values; <sup>b</sup>Overall treatment effect of enpatoran vs placebo based on logistic models; <sup>c</sup>95% confidence intervals showing enpatoran dose vs placebo comparison; <sup>d</sup>CLASI-70 response was defined as a decrease in CLASI of ≥70% from baseline values. **BID**, twice daily; **CLASI**, Cutaneous Lupus Erythematosus Disease Area and Severity Index; **CLASI-A**, CLASI-activity.

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# Safety analysis

Participants, n (%)	Placebo BID (N=95)	Enpatoran 25 mg BID (N=71)	Enpatoran 50 mg BID (N=74)	Enpatoran 100 mg BID (N=114)
<b>Any TEAE</b>	61 (64.2)	43 (60.6)	47 (63.5)	70 (61.4)
<b>Any related TEAE</b>	19 (20.0)	13 (18.3)	19 (25.7)	22 (19.3)
<b>Any Grade <math>\geq</math>3 TEAE</b>	6 (6.3)	1 (1.4)	3 (4.1)	5 (4.4)
<b>Any Grade <math>\geq</math>4 TEAE</b>	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Any TEAE leading to death</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Most common TEAEs by system organ class</b>				
Infections and infestations (139 AEs)	33 (34.7)	27 (38.0)	31 (41.9)	48 (42.1)
Herpes zoster	2 (2.1)	2 (2.8)	2 (2.7)	2 (1.8)
Gastrointestinal disorders (55 AEs)	14 (14.7)	15 (21.1)	10 (13.5)	16 (14.0)
Investigations (41 AEs)	18 (18.9)	7 (9.9)	7 (9.5)	9 (7.9)
<b>Any serious TEAE</b>	3 (3.2)	1 (1.4)	3 (4.1)	5 (4.4)

## Safety analysis, N=354.

AE, adverse event; BID, twice daily; TEAE, treatment-emergent adverse event.

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## Conclusions

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- Enpatoran exhibited nominally significant improvements in BICLA response at Week 24 compared with placebo; however, no statistically significant dose-response relationship for enpatoran was identified
  - Greater treatment effect in participants with active cutaneous manifestations, high IFN-GS or high doses of GC at baseline
- In patients with SLE and active cutaneous manifestations, enpatoran improved CLASI-50 and CLASI-70 responses compared with placebo
  - Adds to evidence from WILLOW Cohort A<sup>1</sup>
- Enpatoran-mediated downmodulation of IFN-GS confirms the involvement of the TLR7/8 pathway in type I IFN pathway activation in SLE
- Enpatoran was well tolerated
  - Safety profile consistent with that observed in previous studies<sup>2,3</sup>

**Results support further investigation of enpatoran in people with lupus**

**BICLA**, British Isles Lupus Assessment Group-based Composite Lupus Assessment; **CLASI**, Cutaneous Lupus Erythematosus Disease Area and Severity Index; **GC**, glucocorticoid; **IFN**, interferon; **IFN-GS**, IFN gene signature; **SLE**, systemic lupus erythematosus; **TLR**, toll-like receptor.

1. Morand E, et al. *LUPUS 2025*. Abstract LBO010; 2. Witte T, et al. *ACR 2024*. Abstract 1553; 3. Port A, et al. *Pharmacol Res Perspect* 2021;9:e00842.

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