

Articles

Enpatoran, a Toll-like receptor 7/8 inhibitor, in moderate-to-severe systemic lupus erythematosus: findings from Cohort B of a multicentre, international, double-blind, placebo-controlled dose-finding phase 2 trial

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Summary

Background Toll-like receptors (TLR) 7 and 8 (TLR7/8) are activators of innate and adaptive immunity contributing to lupus pathogenesis. In Cohort B of WILLOW, a phase 2, randomised, placebo-controlled, double-blind, basket, dose-finding study, enpatoran, an oral small molecule inhibitor of TLR7/8, was evaluated in participants with active systemic lupus erythematosus (SLE).

Methods Participants were eligible if they were aged 18–75 years with moderate-to-severe SLE, with or without cutaneous manifestations, had a disease duration of at least 6 months, and were receiving a stable dose of medication before the screening period. Participants were recruited from 132 centres in 22 countries. In Part 1, participants were randomly allocated in a 1:2 ratio to receive either placebo or 100 mg enpatoran, both twice-daily. Following the enrolment of 60 participants, Part 2 was activated and additional participants were randomly allocated in a 1:1:1:1 ratio to 25 mg, 50 mg, or 100 mg of enpatoran or placebo, all twice-daily, for 24 weeks. Random allocation was stratified by region, biomarker status, and hybrid Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index score. The primary objective was to evaluate the dose–response relationship of enpatoran, using British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response rate at week 24, based on multiple comparison procedure–modelling analysis. Study visits were scheduled from week 0 to week 24, followed by a 2-week safety follow-up period for participants who chose not to enter the long-term extension. From weeks 2 to 12, glucocorticoid doses were tapered to a prednisone-equivalent dose of no more than 5 mg/day, as clinically tolerated. Adverse events were monitored continuously throughout the study; safety parameters (including physical examination, vital signs, and routine chemistry and haematology) were assessed at all study visits. The trial was registered at ClinicalTrials.gov (NCT05162586) and a long-term extension study is ongoing.

Findings Between May 4, 2022, and Feb 6, 2024, participants were screened for eligibility for WILLOW cohorts A and B; 715 participants were screened and 354 were randomly allocated and included in the Cohort B safety population (95 to placebo, 71 to 25 mg enpatoran, 74 to 50 mg enpatoran, and 114 to 100 mg enpatoran). One patient allocated to the placebo group was found to be ineligible and was excluded from the full analysis set for the efficacy analyses. 335 (95%) of 353 participants were female, 18 (5%) were male, and median age was 41 years (IQR 33–51). At week 24, the study did not meet its primary objective of identifying a statistically significant dose–response relationship for enpatoran in BICLA response rate (p=0·14). BICLA response rates at week 24 were higher with all doses of enpatoran (25 mg: 41 [58%] of 71; odds ratio [OR] vs placebo 2·2 [95% CI 1·1–4·0], 50 mg: 36 [49%] of 74; OR 1·5 [95% CI 0·8–2·8], and 100 mg: 56 [49%] of 114; OR 1·6 [95% CI 0·9–2·8]) versus placebo (37 [39%] of 94). The most common treatment-emergent adverse event was diarrhoea, in four (6%) of 71, two (3%) of 74, and two (2%) of 114 participants in the 25 mg, 50 mg, and 100 mg enpatoran groups, respectively, and seven (7%) of 95 participants in the placebo group. Serious adverse events were reported in one (1%) of 71, three (4%) of 74, five (4%) of 114, and three (3%) of 95 participants treated with 25 mg, 50 mg, and 100 mg enpatoran and placebo, respectively.

Interpretation In this study of participants with moderate-to-severe SLE, enpatoran improved BICLA response rates versus placebo; however, the primary objective of a statistically significant dose-dependent effect on disease activity based on BICLA response was not met. Enpatoran was well tolerated across all dose groups.

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Veille bibliographique

WILLOW cohort A

Efficacité et innocuité de l'enpatoran, un inhibiteur des récepteurs Toll-like 7/8,chez les patients présentant des manifestations cutanées du lupus érythémateux cutané ou du lupus érythémateux systémique

Eric F Morand, Victoria P Werth, Joerg Wenzel, Richard Furie, Maria Dall'Era, Jorge Sanchez-Guerrero, Sanjeev Roy, Summer G Goodson, Flavie Moreau, Hans Gühring, Evridiki Sgouroudi, Lena Klopp-Schulze, David R Pearson

Morand EF *et al.* Lancet Rheumatol 2026; Vol 8 (7)

WILLOW A - Enpatoran dans le lupus cutané

Essai multicentrique, en double aveugle, contrôlé par placebo, de phase 2 de recherche de dose

Rationel

- Aucun traitement ciblé approuvé pour le lupus cutané (CLE)
- Hyperactivation locale de l'IFN type I dans la peau lésée et non lésée, or TLR7/8 = inducteurs en amont
- Première démonstration contrôlée d'une inhibition TLR7/8 dans le CLE et l'atteinte cutanée du LES

Critères d'inclusion : lupus cutané ou LES avec atteinte cutanée prédominante

- Adultes 18 – 75 ans, CLE ou LES avec CLASI-A ≥ 8, durée ≥ 6 mois, biopsie ou photo de CLE subaigu ou discoïde
- LES inclus uniquement si activité systémique faible/nulle (BILAG ≤ 1B/C/D)
- Néphrite lupique active exclue

Schéma sur 24 semaines, avec 132 sites, dans 22 pays

- Randomisation 1:1:1:1 → placebo, 25 mg, 50 mg, 100 mg enpatoran BID (n = 100 analysés)
- Standard of care maintenu (antipaludéens, IS, CS, dermocorticoïdes)

Critère de jugement principal

- Relation dose-réponse sur la variation en % du CLASI-A à S16

Morand EF *et al*. Lancet Rheumatol 2026; Vol 8 (7)

Caractéristiques de la population à l'inclusion

WILLOW Cohorte A — 100 patients

	Placebo (n = 26)	Enpa 25 mg (n = 23)	Enpa 50 mg (n = 25)	Enpa 100 mg (n = 26)
Âge médian, ans (IQR)	49 (42–58)	41 (35–53)	47 (35–56)	45 (34–53)
Femmes, n (%)	22 (85)	17 (74)	19 (76)	19 (73)
CLE seul, n (%)	14 (54)	14 (61)	15 (60)	15 (58)
LES + CLE, n (%)	12 (46)	9 (39)	10 (40)	11 (42)
Durée du CLE, ans (SD)	10,9 (11,4)	8,2 (8,1)	7,7 (7,8)	14,2 (11,4)
CLASI-A moyen (SD)	13 (4,3)	12 (4,9)	16 (7,2)	13 (5,2)
CLASI-A sévère (≥ 21), n (%)	3 (12)	1 (4)	5 (20)	4 (15)
CS systémiques, n (%)	15 (58)	12 (52)	18 (72)	14 (54)
Antipaludéens, n (%)	20 (77)	17 (74)	16 (64)	23 (88)
Immunosuppresseurs, n (%)	8 (31)	8 (35)	11 (44)	11 (42)
Échec antérieur d'IS, n (%)	26 (100)	21 (91)	22 (88)	25 (96)

Population à dominante cutanée chronique : 58 % CLE pur (subaigu/discoïde), 42 % LES avec atteinte cutanée. Sévérité modérée prédominante (CLASI-A médian ~ 13).

Résultats — critère principal, secondaires et tolérance

Critère principal et critères secondaires (S16 et S24)

Critère	Placebo	Enpa 25 mg	Enpa 50 mg	Enpa 100 mg	Δ vs PBO (IC 95 %)
ΔCLASI-A à S16, %	**−44**	**−64**	**−68**	**−72**	**−20 / −24 / −28 ; p = 0,0002**
ΔCLASI-A à S24, %	**−43**	**−69**	**−74**	**−79**	**Maintien à S24**
CLA-IGA 0 – 1 à S16, %	**15**	**43**	**40**	**46**	**OR 4 – 5 ; p ≤ 0,02**
CLA-IGA 0 – 1 à S24, %	**27**	**48**	**48**	**58**	**100 mg : OR 3,7 ; p = 0,018**
ΔPGA-CLE à S24	**−23**	**−44**	**−42**	**−46**	**Δ −20 à −24 ; p ≤ 0,001**
Skindex symptômes (S24)	**−14**	**−27**	**−29**	**−22**	**Δ jusqu'à −15**

Tolérance sur 24 semaines

n (%)	PBO (n=26)	25 mg (n=24)	50 mg (n=26)	100 mg (n=26)
EI les + fréquents : IVRS	2 (8)	2 (8)	4 (15)	5 (19)
EI graves	1 (4)	2 (8)	0	1 (4)
EI cutanés	—	stable	stable	stable
Arrêt du ttt pour EI	1 (4)	0	1 (4)	2 (8)
Décès	0	0	0	0

Profil de tolérance comparable au placebo. Pas de signal pour les EI sévères ou les EI cutanés indésirables.

Critère principal ATTEINT : relation dose-réponse significative sur le CLASI-A à S16

Effet précoce (dès S2), durable (S24), cohérent sur tous les critères dermatologiques.

Suppression marquée de l'IFN-GS dès S2 (cohérent avec le mécanisme TLR7/8).

Morand EF *et al*. Lancet Rheumatol 2026; Vol 8 (7)

Conclusion et perspective

Ce que démontre WILLOW Cohorte A

Critère principal ATTEINT : relation dose-réponse significative sur le CLASI-A à S16 (p = 0,0002)

- Toutes les doses supérieures au placebo : ΔCLASI-A −64 à −72 % vs −44 %

Bénéfice multidomaine (peau)

- PGA-CLE, CLA-IGA, Skindex symptômes : tous améliorés

Effet précoce et durable

- Séparation des courbes dès S2, maintenue jusqu'à S24

Mécanisme cohérent

- Suppression rapide de l'IFN-GS dès S2 (réduction de >50 % à 100 mg)

Bonne tolérance (zéro arrêt, zéro décès)

→ Phase 3 dans le CLE attendue

Perspective

Commentaire C. Arriens
Lancet Rheumatol 2026

- Premier essai contrôlé positif d'un anti-TLR 7/8 dans le lupus
- Absence de réponse strictement linéaire au-delà de 25 mg : précédents similaires avec deucravacitinib et anifrolumab en faveur de possibles boucles de rétro-contrôle
- Petits effectifs par groupe (~ 25), limitant la différenciation entre doses
- Lupus = forte hétérogénéité, taux de réponse placebo élevés nécessitant une vigilance dans l'interprétation

Morand EF *et al*. Lancet Rheumatol 2026; Vol 8 (7)