

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 B

Enpatoran, un inhibiteur des récepteurs Toll-like 7/8,dans le lupus érythémateux systémique modéré à sévère

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

Willow Cohorte B

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

Rationel

- TLR 7/8 = senseurs d'acides nucléiques en amont de la signalisation interféron de type I et de l'activation B
- Mutations gain-de-fonction de TLR7 → lupus monogénique de l'enfant ; inhibition TLR7/8 = nouvelle cible
- Enpatoran : petite molécule orale, premier inhibiteur sélectif TLR7/8 testé en phase 2 dans le lupus

Critères d'inclusion : LES modéré à sévère

- Adultes 18 – 75 ans avec LES (SLICC ou EULAR/ACR 2019), durée ≥ 6 mois, traitement stable
- Activité modérée-sévère : BILAG 2004 ≥ 1A ou ≥ 2B ; SELENA-SLEDAI ≥ 6 ou CLASI-A ≥ 8

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

- Part 1 (n = 61) : 1/2 placebo vs enpatoran 100 mg 2x/j
- Part 2 (n = 293) : 1:1:1:1 placebo vs 25 / 50 / 100 mg 2x/j
- Décroissance imposée des corticoïdes à ≤ 5 mg/j entre S2 et S12

Critère de jugement principal

- Relation dose – réponse sur le taux de répondeurs BICLA à S24

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Caractéristiques de la population à l'inclusion

WILLOW Cohorte B — 353 patients

	Placebo (n = 94)	Enpa 25 mg (n = 71)	Enpa 50 mg (n = 74)	Enpa 100 mg (n = 114)
Âge médian, ans (IQR)	40 (34–51)	41 (32–49)	39 (29–48)	44 (36–53)
Femmes, n (%)	87 (93)	69 (97)	69 (93)	110 (96)
Durée du LES, ans (SD)	10,2 (7,8)	7,0 (6,9)	9,8 (7,8)	9,6 (6,6)
Manifestations cutanées (SLE+CLE), n (%)	59 (63)	45 (63)	43 (58)	69 (61)
Signature IFN haute, n (%)	67 (71)	54 (76)	50 (68)	83 (73)
Hybrid SELENA-SLEDAI moyen	11 (3,3)	11 (2,9)	10 (2,8)	11 (3,0)
BILAG sévère (≥ 1A), n (%)	35 (37)	23 (32)	28 (38)	45 (39)
Corticoïdes systémiques, n (%)	78 (83)	63 (89)	66 (89)	94 (82)
dont ≥ 10 mg/j prednisone-équiv.	51 (54)	34 (48)	36 (49)	59 (52)
Immunosuppresseurs, n (%)	50 (53)	42 (59)	46 (62)	66 (58)
Antipaludéens, n (%)	80 (85)	60 (85)	60 (81)	97 (85)

Population représentative de LES modéré à sévère, biomarqueurs IFN-haut majoritaires (72 %), forte exposition aux corticoïdes (51 % à ≥ 10 mg/j).

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Résultats — critère principal, secondaires et tolérance

Critère principal et critères secondaires (S24, full analysis set)

Critère	Placebo	Enpa 25 mg	Enpa 50 mg	Enpa 100 mg	OR vs PBO (IC 95 %)
BICLA à S24, %	39	**58**	49	49	**25 mg : 2,2 (1,1 – 4,0) ; p = 0,009**
BICLA + épargne CS, %	31	**59**	**56**	48	**Δ jusqu'à 28 pts (25 mg)**
Réponse SRI-4, %	53	62	65	**68**	**100 mg : 1,9 (1,1 – 3,5) ; p = 0,012**
Atteinte LLDAS, %	25	30	**43**	31	**50 mg : 2,5 (1,3 – 4,9) ; p = 0,004**
Rémission DORIS, %	11	10	11	18	100 mg : 2,0 (0,9 – 4,6) ; p = 0,049
BICLA sous-grpe IFN-haut, %	31	**61**	**52**	**49**	**25 mg : 3,4 (1,6 – 7,3) ; p = 0,001**

Tolérance sur 24 semaines

n (%)	PBO (n=95)	25 mg (n=71)	50 mg (n=74)	100 mg (n=114)
≥ 1 EI	64%	61%	64%	61%
EI graves	3 (3)	1 (1)	3 (4)	5 (4)
Diarrhée (le plus fréquent)	7 (7)	4 (6)	2 (3)	2 (2)
Poussée modérée/ sévère (BILAG)	12 (13)	4 (6)	5 (7)	8 (7)
Décès	0	0	0	0

Tolérance globale comparable au placebo — pas de signal nouveau. Suppression rapide de l'IFN-GS dès S2, maintenue à S24.

Le critère principal n'est pas atteint (p = 0,14, MCP-Mod) mais effet positif sur tous les critères secondaires

Effet le plus net dans les sous-groupes IFN-haut et CS ≥ 10 mg/j (OR jusqu'à 3,5). Le 25 mg semble cliniquement comparable au 100 mg.

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Conclusion et perspective

Ce que démontre WILLOW Cohorte B

Critère principal NON atteint (relation dose-réponse, p = 0,14)
Mais réponse BICLA améliorée par toutes les doses vs placebo (49 – 58 % vs 39 %)

Effet le plus marqué chez les patients
IFN-haut (OR jusqu'à 3,4)
fortement corticodépendants (≥ 10 mg/j ; OR 3,5)
avec atteinte cutanée (CLASI-A améliorée significativement)

Suppression rapide et profonde de l'IFN-GS dès S2
Validation mécanistique du concept TLR7/8 → interféron de type I

Bonne tolérance, comparable au placebo, sans signal inattendu
→ Phase 3 prévue, sans doute centrée sur la dose 25 mg

Perspective

Commentaire McCann & Durcan
Lancet 2026 ; 407 : 1761

- Premier essai contrôlé de l'inhibition TLR7/8 dans le LES, signaux de sécurité rassurants
- Confirme une cible thérapeutique d'intérêt, en particulier chez les patients avec atteinte cutanée et fortement corticodépendants
- Faible représentation des patients noirs (population à inclure dans la phase 3)
- À situer dans un paysage en évolution : litifilimab, deucravacitinib, ianalumab