Safety, Pharmacokinetics, and Pharmacodynamics of Single Oral Enpatoran Doses in a Phase I Study of Healthy Japanese and Caucasian Participants: Feasibility of Including Asian Participants in a Phase II Study of Enpatoran

Sathej Gopalakrishnan[1], Axel Krebs-Brown[2], Marco Nogueira Filho[1], Yoshihiro Kuroki[3], Angelika Bachmann[1], Andreas Becker[1], Frank Schippers[4], Markus Fluck[1], Özkan Yalkinoglu[1], Christine Kleinmond[5], Denesh Chitkara[6], **Cristina Vazquez-Mateo[6]**, Sanjeev Roy[7], Lena Klopp-Schulze[1]

[1]Translational Medicine, the healthcare business of Merck KGaA, Darmstadt, Germany; [2]Global Biostatistics, the healthcare business of Merck KGaA, Darmstadt, Germany; [3]Translational Medicine, Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany; [4]Global Patient Safety, the healthcare business of Merck KGaA, Darmstadt, Germany; [5]Global Clinical Development, the healthcare business of Merck KGaA, Darmstadt, Germany; [6]Global Clinical Development, EMD Serono, Billerica, MA, USA; [7]Global Clinical Development, Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany

CONCLUSIONS

These ethno-bridging study results support an **Asia-inclusive global development program** for enpatoran, including the **recently initiated WILLOW Phase II study** (NCT05162586; see below)[1]

A single dose of enpatoran up to 300 mg was well tolerated in healthy Japanese and Caucasian participants

No interethnic differences were observed across PK, PD and safety parameters and results were generally in agreement with the first-in-human study[2]

INTRODUCTION

- Enpatoran is a novel, **highly selective** and potent dual **TLR7 and TLR8 inhibitor**
- Enpatoran may treat **autoimmune disorders** including SLE and CLE
- In a first-in-human study in healthy participants, enpatoran was **well tolerated** and showed a **linear PK profile[2]**

OBJECTIVES

To evaluate and compare safety and PK of single doses of enpatoran in Japanese and Caucasian participants

To explore the *ex-vivo* PD effects of single dose administration of enpatoran

WILLOW SLE/CLE Phase II Study

Scan for WILLOW study design

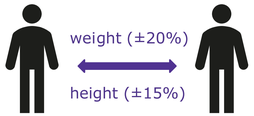
Copies of the study design obtained are for personal use only and may not be reproduced without written permission of the authors

Please also see published EULAR 2022 abstract:
Morand E, et al. *Ann Rheum Dis.* 2022;Suppl:AB0444[1]

METHODS

Single-center, open-label, sequential ascending dose group Phase I study in healthy Japanese and Caucasian participants

Japanese and Caucasian participants were matched



100, 200 or 300 mg enpatoran single dose; orally administered as a tablet formulation (fasted conditions)

Safety: assessed from Day -1 to Day 8
PK parameters: calculated post-dose from Day 1–3 using non-compartmental analysis
Exposure: ANCOVA model with ethnic group, natural log-transformed dose, and ethnic group by natural log dose interaction as fixed effect
***Ex-vivo* cytokine (IL-6) secretion:** assessed under stimulated (using the TLR7/8 agonist, R848) and unstimulated conditions pre- and post-dose

RESULTS

Participants

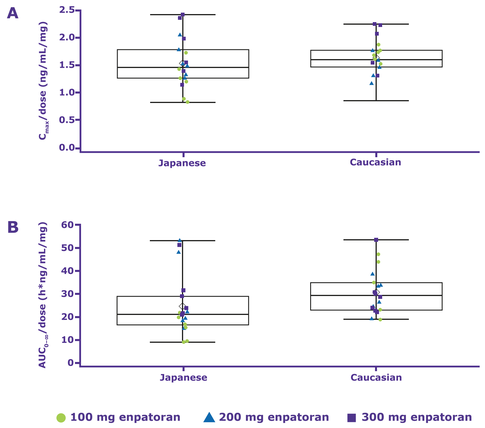
- 36 male participants: 18 Japanese and 18 Caucasian
- Mean (SD) age was 35 (±11) years
- Mean (SD) body mass index was 23 (±2) kg/m²

Pharmacokinetics

Enpatoran exposure was comparable between the two ethnic groups and appeared **dose-proportional**

Japanese/Caucasian Geo LS means (90% CI):
- C_{max} = 0.94 (0.79–1.13)
- $AUC_{0-\infty}$ = 0.90 (0.75–1.07)

Dose-normalized A) C_{max} and B) $AUC_{0-\infty}$ by ethnic group



The upper and lower edges of the box represent the first and third quartile, the upper and lower whiskers represent the minimum and maximum. The solid line in the box is the median, and the diamond denotes the mean.

Safety and tolerability

A total of **17 TEAEs were reported** by 6 Japanese and 4 Caucasian participants
- Most (14) of the TEAEs were mild
- Eight of the TEAEs were considered treatment related; all were mild to moderate

Number (%) participants	100 mg		200 mg		300 mg	
	J n=6	C n=6	J n=6	C n=6	J n=6	C n=6
TEAEs	0	1 (17)	3 (50)	0	3 (50)	3 (50)
Treatment-related TEAEs	0	1 (17)*	2 (33)†	0	2 (33)*	1 (17)‡

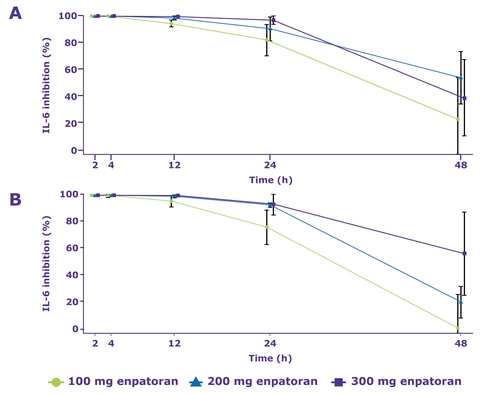
*mild diarrhea; †mild flatulence; ‡moderate headache
C, Caucasian; **J,** Japanese

There were **no serious AEs or deaths** during the study, and **no participant discontinued** due to a treatment-related TEAE

Pharmacodynamics

Enpatoran **effectively inhibited *ex vivo*-stimulated cytokine release,** with high inhibition levels (76–97%) sustained over 24 hours in a dose-dependent manner

Arithmetic mean IL-6 inhibition over time in A) Japanese and B) Caucasian participants



Abbreviations: ANCOVA, analysis of covariance; **$AUC_{0-\infty}$**, area under the plasma concentration–time curve from time 0 to infinity; **AEs**, adverse events; **CI**, confidence interval; **CLE**, cutaneous lupus erythematosus; **C_{max}**, maximum plasma concentration; **Geo LS Mean**, geometric least squares mean; **IL-6**, interleukin-6; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **TEAE**, treatment-emergent adverse event; **SD**, standard deviation; **SLE**, systemic lupus erythematosus; **TLR**, toll-like receptor

References: 1. Morand E, et al. *Ann Rheum Dis.* 2022;Suppl:AB0444; 2. Port A, et al. *Pharmacol Res Perspect.* 2021;9(5):e00842.
We would like to thank those who took part in this study. The study was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945). Medical writing support was provided by Bioscript Stirling Ltd and Editorial support was provided by Rahul Birari and Bitumani Borah of Merck Specialties Pvt. Ltd., Bangalore, India, an affiliate of Merck KGaA, Darmstadt, Germany.
Author disclosures: ABr, SG and **MF** are employees and shareholders of the healthcare business of Merck KGaA, Darmstadt, Germany. **ABm, AK-B, FS, LKS, CK** and **MNF** are employees of the healthcare business of Merck KGaA, Darmstadt, Germany and **ÖY** was an employee of the healthcare business of Merck KGaA, Darmstadt, Germany at the time of the study. **YK** is an employee of Merck Biopharma Co. Ltd, an affiliate of Merck KGaA, Darmstadt, Germany; **DC** and **CVM** are employees of EMD Serono, Billerica, MA, USA; **SR** is an employee of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.
Presented at the American College of Rheumatology Convergence 2022 | 10–14 November 2022 | Philadelphia, Pennsylvania In person and Virtual
Correspondence: cristina.vazquez-mateo@emdserono.com

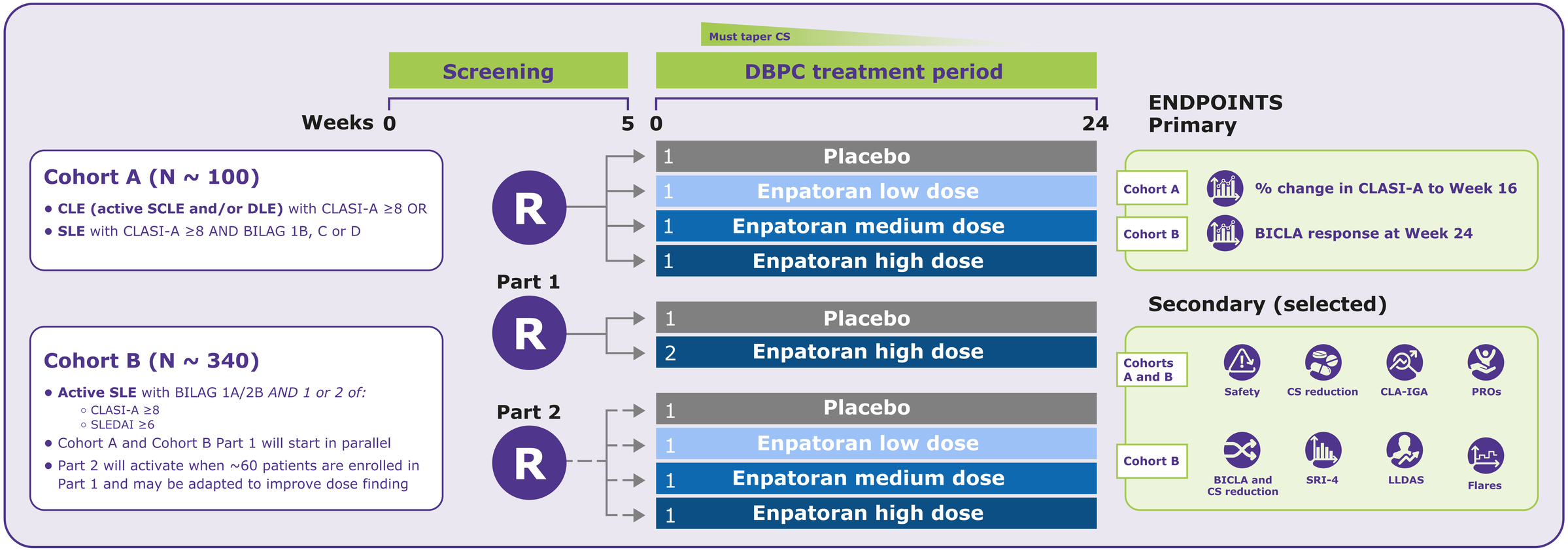
Safety, Pharmacokinetics, and Pharmacodynamics of Single Oral Enpatoran Doses in a Phase I Study of Healthy Japanese and Caucasian Participants: Feasibility of Including Asian Participants in a Phase II Study of Enpatoran

Sathej Gopalakrishnan[1], Axel Krebs-Brown[2], Marco Nogueira Filho[1], Yoshihiro Kuroki[3], Angelika Bachmann[1], Andreas Becker[1], Frank Schippers[4], Markus Fluck[1], Özkan Yalkinoglu[1], Christine Kleinmond[5], Denesh Chitkara[6], **Cristina Vazquez-Mateo**[6], Sanjeev Roy[7], Lena Klopp-Schulze[1]

[1]Translational Medicine, the healthcare business of Merck KGaA, Darmstadt, Germany; [2]Global Biostatistics, the healthcare business of Merck KGaA, Darmstadt, Germany; [3]Translational Medicine, Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany; [4]Global Patient Safety, the healthcare business of Merck KGaA, Darmstadt, Germany; [5]Global Clinical Development, the healthcare business of Merck KGaA, Darmstadt, Germany; [6]Global Clinical Development, EMD Serono, Billerica, MA, USA; [7]Global Clinical Development, Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany

ADDITIONAL CONTENT: WILLOW study design for lupus

WILLOW TRIAL: Global Phase II, basket proof-of-concept, dose-finding, randomized, double-blind, placebo-controlled 24-week study with two lupus cohorts (NCT05162586)[1]
Please see published EULAR 2022 abstract: Morand E, et al. *Ann Rheum Dis.* 2022;Suppl:AB0444



Abbreviations: BICLA, BILAG-Based Composite Lupus Assessment; **BILAG**, British Isles Lupus Assessment Group; **CLA-IGA**, Cutaneous Lupus Activity Investigator's Global Assessment; **CLASI**, Cutaneous Lupus Erythematosus Disease Area and Severity Index; **CLE**, cutaneous lupus erythematosus; **CS**, corticosteroids; **DBPC**, double-blind placebo-controlled; **DLE**, discoid lupus erythematosus; **LLDAS**, Lupus Low Disease Activity State; **PROs**, patient reported outcomes; **R**, randomized; **SCLE**, subacute cutaneous lupus erythematosus; **SLE**, systemic lupus erythematosus; **SLEDAI**, Systemic Lupus Erythematosus Disease Activity Index; **SRI-4**, SLE Responder Index-4

References: 1. EMD Serono Research & Development Institute, Inc. The WILLOW Study With M5049 in SLE and CLE (SCLE and/or DLE) (WILLOW). ClinicalTrials.gov (2022). Available at: https://clinicaltrials.gov/ct2/show/NCT05162586
We would like to thank those who took part in this study. The study was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945). Medical writing support was provided by Bioscript Stirling Ltd and Editorial support was provided by Rahul Birari and Bitumani Borah of Merck Specialties Pvt. Ltd., Bangalore, India, an affiliate of Merck KGaA, Darmstadt, Germany.
Author disclosures: ABr, SG and **MF** are employees and shareholders of the healthcare business of Merck KGaA, Darmstadt, Germany. **ABm, AK-B, FS, LKS, CK** and **MNF** are employees of the healthcare business of Merck KGaA, Darmstadt, Germany and **ÖY** was an employee of the healthcare business of Merck KGaA, Darmstadt, Germany at the time of the study. **YK** is an employee of Merck Biopharma Co. Ltd, an affiliate of Merck KGaA, Darmstadt, Germany; **DC** and **CVM** are employees of EMD Serono, Billerica, MA, USA; **SR** is an employee of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

Presented at the American College of Rheumatology Convergence 2022 | 10–14 November 2022 | Philadelphia, Pennsylvania In person and Virtual

Correspondence: cristina.vazquez-mateo@emdserono.com