P0815

Oral α4β7 integrin antagonist EA1080 (NSHO-101) shows target engagement and α4β7 integrin receptor occupancy following once-daily administration in healthy volunteers

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Background

- EA1080 (NSHO-101) is an oral, small-molecule, selective α4β7 integrin antagonist under development for treatment of inflammatory bowel disease (Table 1).
- EA1080 was safe and well tolerated, and resulted in near-complete inhibition of mucosal addressin cell adhesion molecule-1 (MAdCAM-1) binding to α4β7 integrin (α4β7 receptor occupancy) on peripheral blood CD4⁺ T cells following twice-daily administration of Formulation X², in a phase 1 study in healthy volunteers (DDW 2024: Su1789; NCT04223960).
- Pharmacokinetics (PK) and α4β7 receptor occupancy results from a once-daily formulation are presented here.

Table 1. Inhibitory activity of EA1080 and EA1080-M *in vitro*

In vitro
✓ EA1080-M is a highly potent α4β7 integrin-selective antagonist.
✓ Affinity for α4β7 is more than 12,000 times greater than for α4β1.

Species	System (integrin vs. ligand)		Cell	IC_{50} value [nmol/L]	
				EA1080-M	EA1080
Human	α4β7	vs. MAdCAM-1	RPMI-8866	0.91 ± 0.12	570 ± 270
	α4β1	vs. VCAM-1	Jurkat	11000 ± 8000	> 140000
	α4β7	vs. MAdCAM-1	Whole blood	3.4 ± 1.7*	NT

Integrin-expressing cultured cells or human whole blood were pretreated with compounds, and bound to MAdCAM-1 or VCAM1 (ligands for α4β7 or α4β1 integrin, respectively), and inhibition rates were evaluated.
NT: not tested
Each value is the mean±SEM of values from three independent experiments, except for *, which is from one experiment using blood from three healthy human donors.

REFERENCES *Crohns Colitis.* 2013 Dec;7(11):e533-42

Methods

- PK and α4β7 receptor occupancy results from multiple ascending dose (MAD) cohorts with a formulation for once-daily administration (Formulation D) were assessed in a phase 1 study in healthy volunteers (DDW2024: Su1789; NCT04223960).
- 300 and 800 mg QD with Formulation D, and 100, 200 and 400 mg BID with Formulation X² were assessed (6 subjects per dose).
- Peripheral blood lymphocyte counts were assessed throughout the administration period.

Results

PK and pharmacodynamics (PD)

- Plasma concentrations of active metabolite of EA1080 (EA1080-M) reached steady state within 3-4 days, correlating with maximal inhibition of MAdCAM-1 binding (α4β7 receptor occupancy ; Figure 1, 2).
- Once-daily administration of EA1080 (NSHO-101) with Formulation D resulted in sustained, near-complete inhibition of MAdCAM-1 binding to α4β7 integrin on peripheral blood CD4⁺ T cells (≥95% α4β7 receptor occupancy) during the administration interval (24 hours). This correlated with plasma concentration of EA1080-M, and approximated the receptor occupancy found with twice-daily administration of Formulation X² (Figure 2, 3).
- EA1080-M remained above IC90 MAdCAM-1 binding inhibition concentration levels for >72 hours after the last dose of 800 mg QD with Formulation D and 400 mg BID with Formulation X² (Figure 4).

Figure 1. Plasma concentration of active EA1080-M after repeated administration
Geometric mean trough concentration with QD (Formulation D) and BID (Formulation X²)

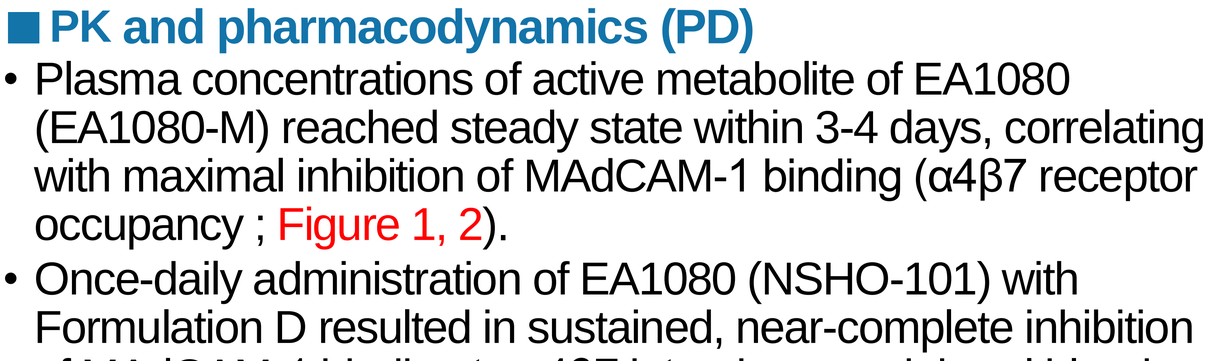


Figure 2. PD time-course profile of EA1080
Percent change in MAdCAM-1 binding rate from baseline in peripheral blood CD4⁺ T Cells with QD (Formulation D) and BID (Formulation X²) at trough.

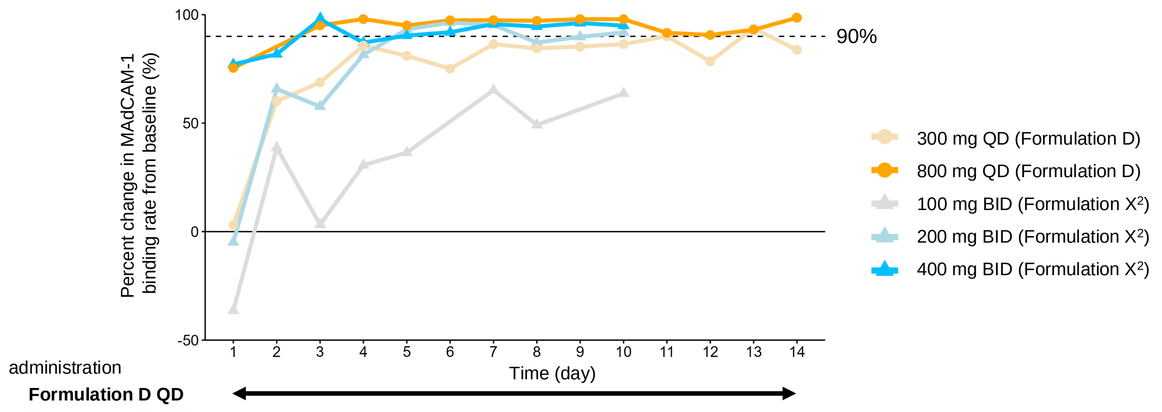
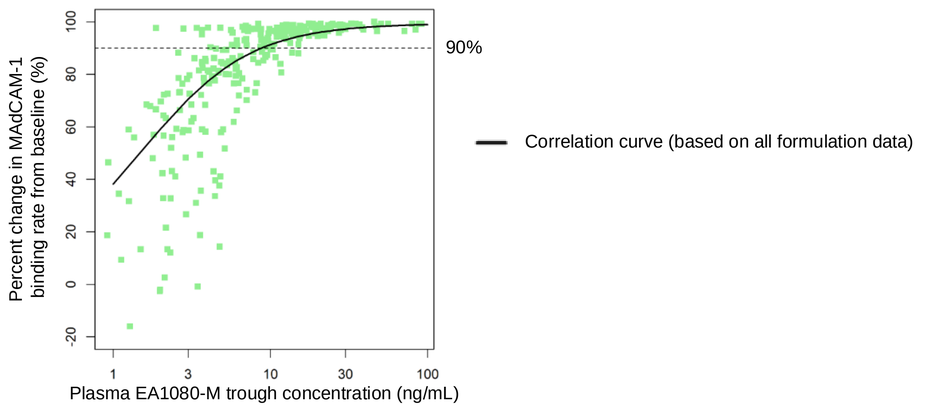


Figure 3. PK-PD relationship
Percent change in MAdCAM-1 binding rate from baseline (%) versus plasma EA1080-M trough concentration (Formulation D, Formulation X²)



Peripheral lymphocyte counts

- No consistent trend in peripheral blood lymphocyte counts was found during the administration period, and the counts had not increased even at t_{max} (Table 2, Figure 4, 5).

Table 2. PK profiles of EA1080-M

	C_{max} (ng/mL)	t_{max}† (h)	$t_{1/2}$ (h)	AUC_{0-24} (ng*h/mL)	C_{trough} (ng/mL)
Formulation D					
300 mg QD	10.0	4.53	21.5	159	5.46
800 mg QD	22.0	8.50	38.0	413	15.7
Formulation X²					
	C_{max} (ng/mL)	t_{max}† (h)	$t_{1/2}$ (h)	AUC_{0-12} (ng*h/mL)	C_{trough} (ng/mL)
100 mg BID	9.36	3.50	14.3	60.4	5.21
200 mg BID	20.1	3.50	34.9	152	10.3
400 mg BID	31.0	2.50	15.4	209	21.0

Geometric mean of PK parameters on final administration day with QD (Formulation D) and BID (Formulation X²).
†Median of t_{max} is shown.

Figure 4. Plasma concentration of active EA1080-M after final administration day
Geometric mean concentration on final administration day with QD (Formulation D) and BID (Formulation X²)

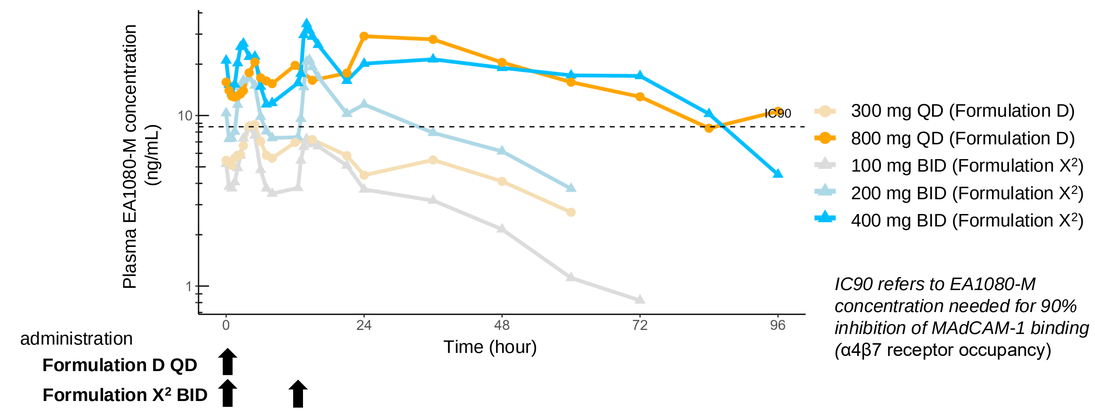
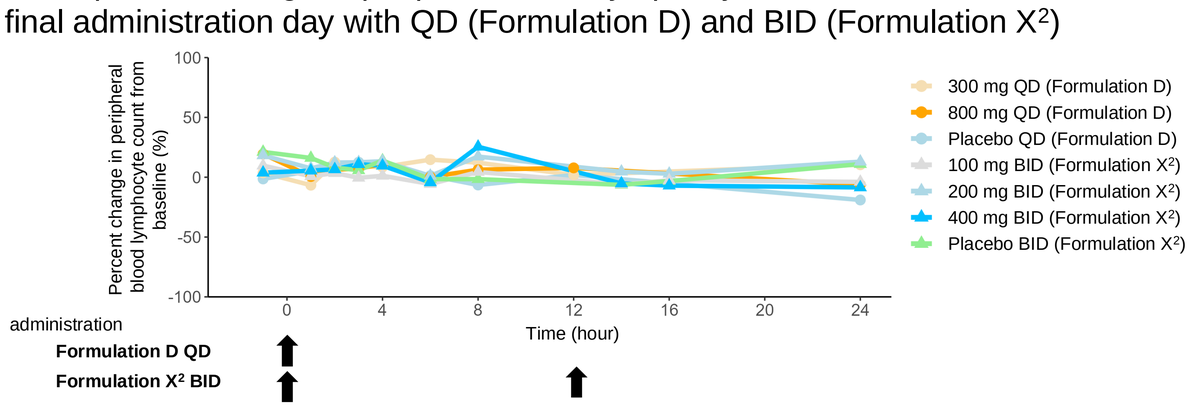


Figure 5. Change of peripheral blood lymphocyte count after final administration day
Mean percent change of peripheral blood lymphocyte count from baseline on final administration day with QD (Formulation D) and BID (Formulation X²)



Safety

- No drug-related TEAEs, serious TEAEs, or drug-related serious TEAEs were reported with Formulation D or X².

Conclusion

- Once-daily oral administration of EA1080 (NSHO-101) results in near-complete inhibition MAdCAM-1 binding to α4β7 integrin (≥95% α4β7 receptor occupancy) during the administration interval.
- No effect on peripheral blood lymphocyte counts was found during the administration period, confirming no specific engagement of α4β1.
- These results support continued development of a once-daily dosing formulation for investigation in clinical studies.