



A0379

ADS024, a single strain live biotherapeutic product, reduces colonic inflammation in DSS-induced colitis when dosed twice daily

Laurent Chesnel, PhD and Susan Acton, PhD
Adiso Therapeutics, Inc.



Introduction

Colonic inflammation is a hallmark of ulcerative colitis (UC), a disease characterized by a dysregulated immune response to gut microbiota. ADS024, an orally administered single strain live biotherapeutic product (SS-LBP), was previously shown to reduce disease activity in mice exposed to dextran sodium sulfate (DSS)¹. ADS024 is currently being developed for the treatment of patients with mild to moderate UC.

1. ADS024 attenuates weight loss and decreases disease activity in DSS-induced colitis L. Chesnel, S. Acton. European Crohn's and Colitis Organisation conference (ECCO), Vienna, 2022. P080.

Methods

Colitis was induced in mice by 3% DSS in drinking water from Day 0 to Day 5; 6 sham mice did not receive DSS (Table 1). Mice were dosed by oral gavage with ADS024 (n=15 per group) twice daily for 7 days, from Day 6 to Day 12, with either 5x10⁸ CFU/dose or 5x10⁴ CFU/dose, or once daily with ADS024 at 1x10⁹ CFU/dose or 1x10⁵ CFU/dose. Negative control mice were dosed with vehicle (PBS; n=20) and a comparator group was dosed with anti-p40 mAb (n=10) once daily (IP) on Days 6, 9, 12. All mice were monitored daily for weight loss, diarrhea, blood in stool, and activity level and individually scored using the Disease Activity Index (DAI) scoring scheme shown below. On Day 12, all mice were sacrificed, and colons collected. Colonic cytokines and myeloperoxidase levels were quantified by ELISA.

Score	Disease Activity Index Scoring Scheme			Endoscopy Scoring Scheme	
	Weight Loss	Diarrhea	Blood in Stool	Colitis Severity	Stool Consistency
0	0.0-4.99%	Normal	Not Present	Normal	Normal, well-formed pellet
1	5.0-9.99%	-	-	Loss of vascularity	Loose stool, soft, staying in shape
2	10.0-14.99%	Loose Stools	Blood Observed	Loss of vascularity and friability	Loose stool, abnormal form with excess moisture
3	15.0-19.99%	-	-	Friability and erosions	Watery or diarrhea
4	>20.0%	Diarrhea	Gross Bleeding	Ulcerations and bleeding	Bloody diarrhea
5	>30.0%	-	-	-	-

Animals underwent video endoscopy on Day 12 to assess colitis severity and stool consistency and were individually scored on a 4-point scale using the endoscopy scoring scheme shown above.

Results

DSS-exposed animals treated with ADS024 twice daily at higher dose (5x10⁸ CFU/dose) demonstrated significant attenuation of weight loss (p<0.05) (Figure 1) and decreased composite Disease Activity Index (DAI) (p<0.01) (Figure 2) compared to control (DSS only) animals. This ADS024 dosing regimen also decreased mean colon weight:length ratio, a measure of inflammation, as compared to controls (p<0.005) (Figure 3).

The anti-p40 mAb, with a mechanism of action similar to ustekinumab, an approved treatment for UC, reduced DAI but did not significantly reduce colon weight:length ratio. Once daily dosing of ADS024 at higher daily dose (1x10⁹ CFU given in the morning) was ineffective, despite the same total daily dose as responding mice dosed BID. A much lower daily dose (1x10⁵ CFU/day) was ineffective regardless of dosing schedule.

In DSS-exposed mice treated twice daily with higher dose ADS024, the inflammatory marker interleukin-6 (IL6) was significantly down in colons and both interleukin 1 beta (IL1b) and colonic myeloperoxidase (MPO), a measure of active neutrophils, trended down (Figure 4).

Conclusions

Oral treatment with higher dose ADS024 twice daily, but not once daily, improved disease activity index and reduced measures of inflammation including colon weight:length ratio and the inflammatory cytokine IL-6.

DSS Study Design

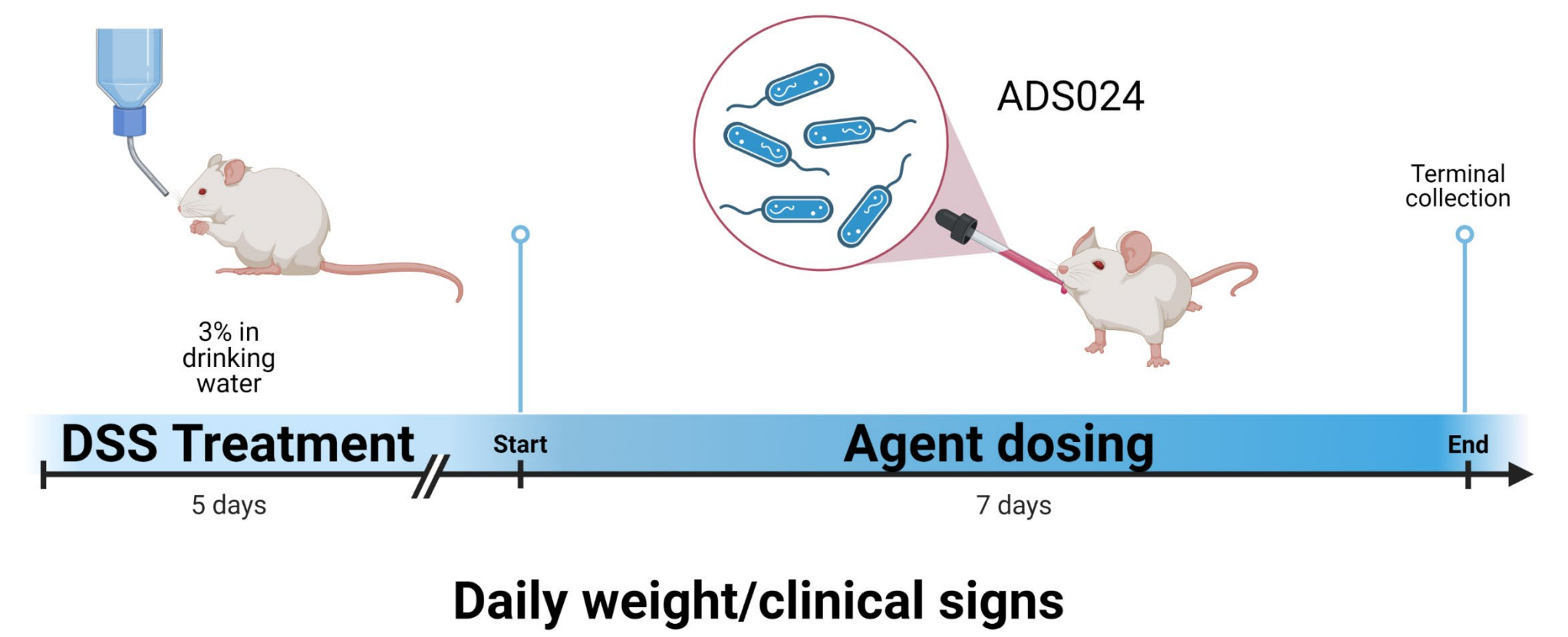


Table 1: Study design of DSS-induced colitis murine model

Group	Number of mice	DSS	Treatment	Dose	Daily	Schedule	Route	DAI Scoring	Terminal Collections
Naive	6	--	--	--	--	--	--		
Vehicle	20		PBS	--	--				
ADS024 - 5E4 CFU BID	15 per group	3% DSS (Days 0-5)	ADS024	5x10 ⁴ CFU	BID	Days 6-12	PO	QD	Day 12
ADS024 - 5E8 CFU BID				5x10 ⁸ CFU	BID				
ADS024 - 1E5 CFU QD				1x10 ⁵ CFU	QD				
ADS024 - 1E9 CFU QD				1x10 ⁹ CFU	QD				
Anti-p40	10		Anti-p40 mAb	10 mg/kg	QD	Days 6, 9, 12	IP		

Fig 1. High dose (5x10⁸ CFU) ADS024 given twice daily, but not once daily, attenuates DSS-mediated weight loss

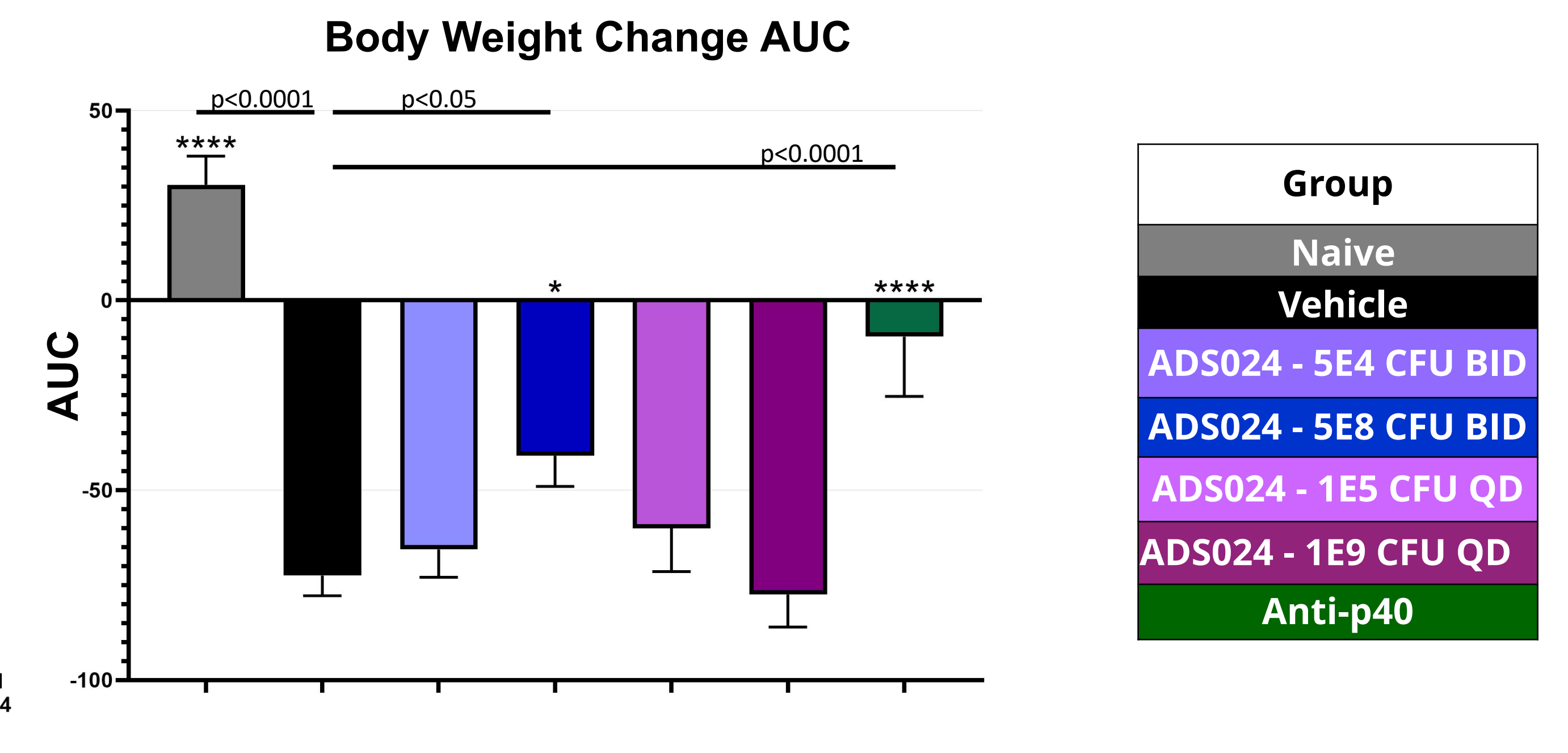
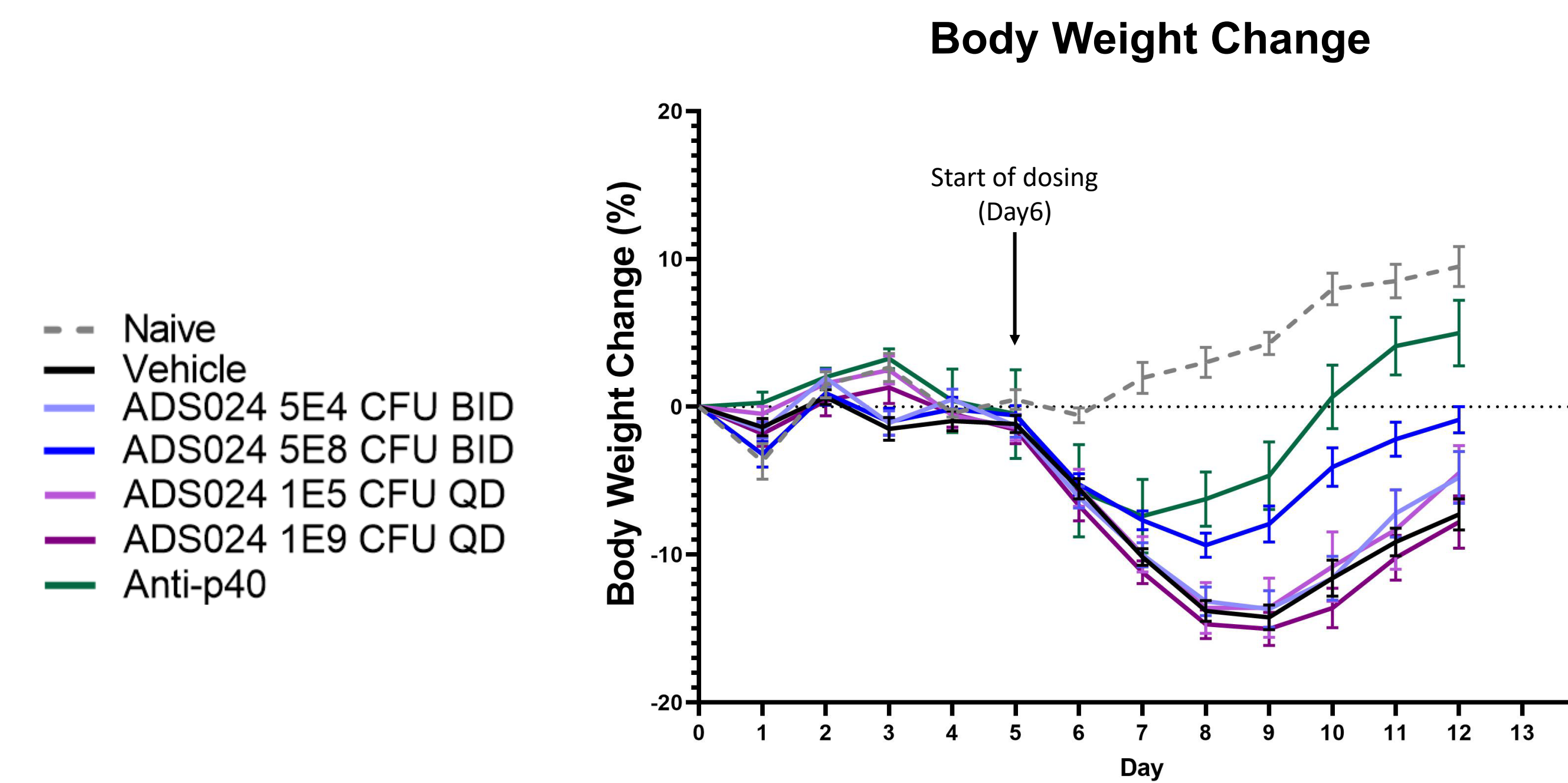


Fig 2. High dose ADS024 given twice daily attenuates DSS-mediated disease activity

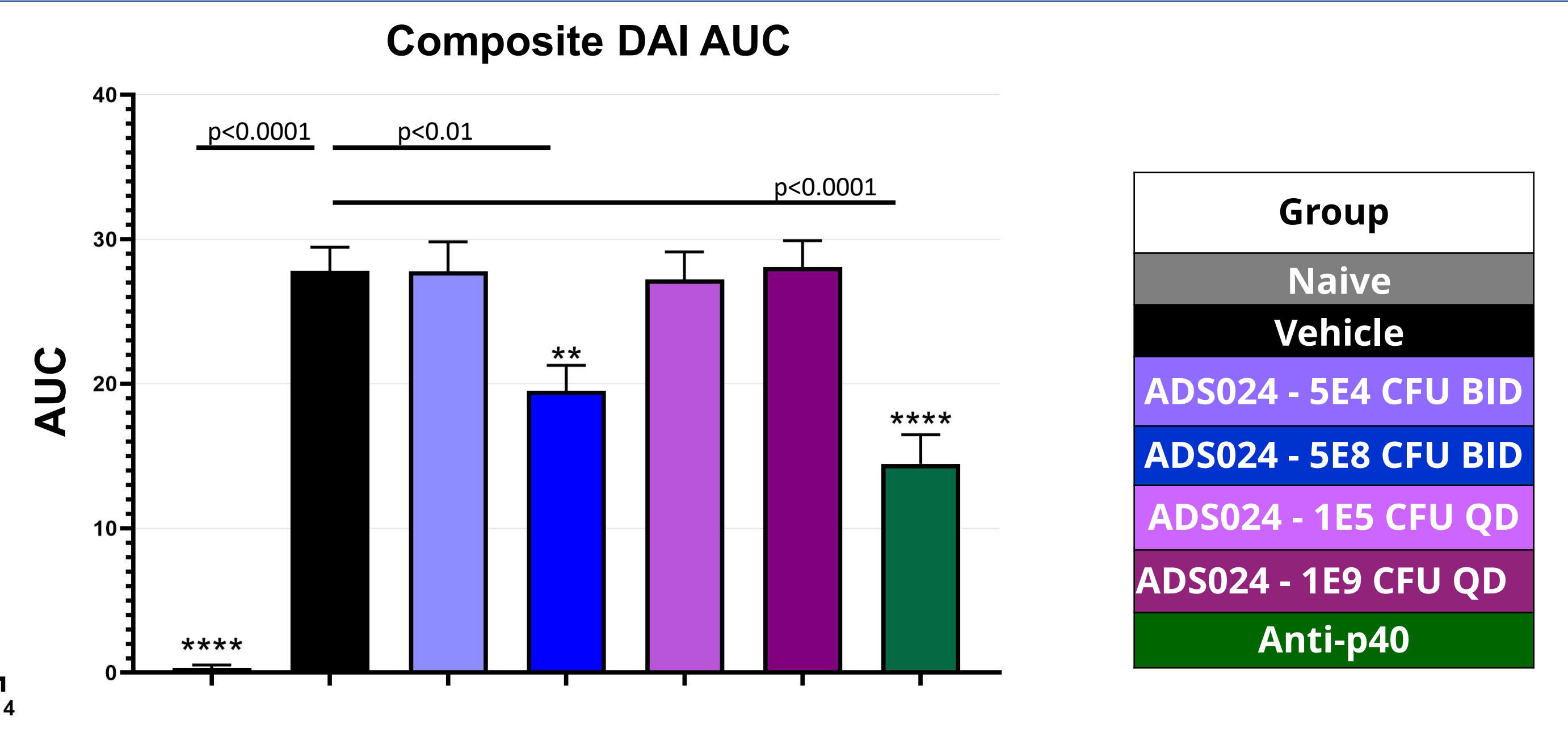
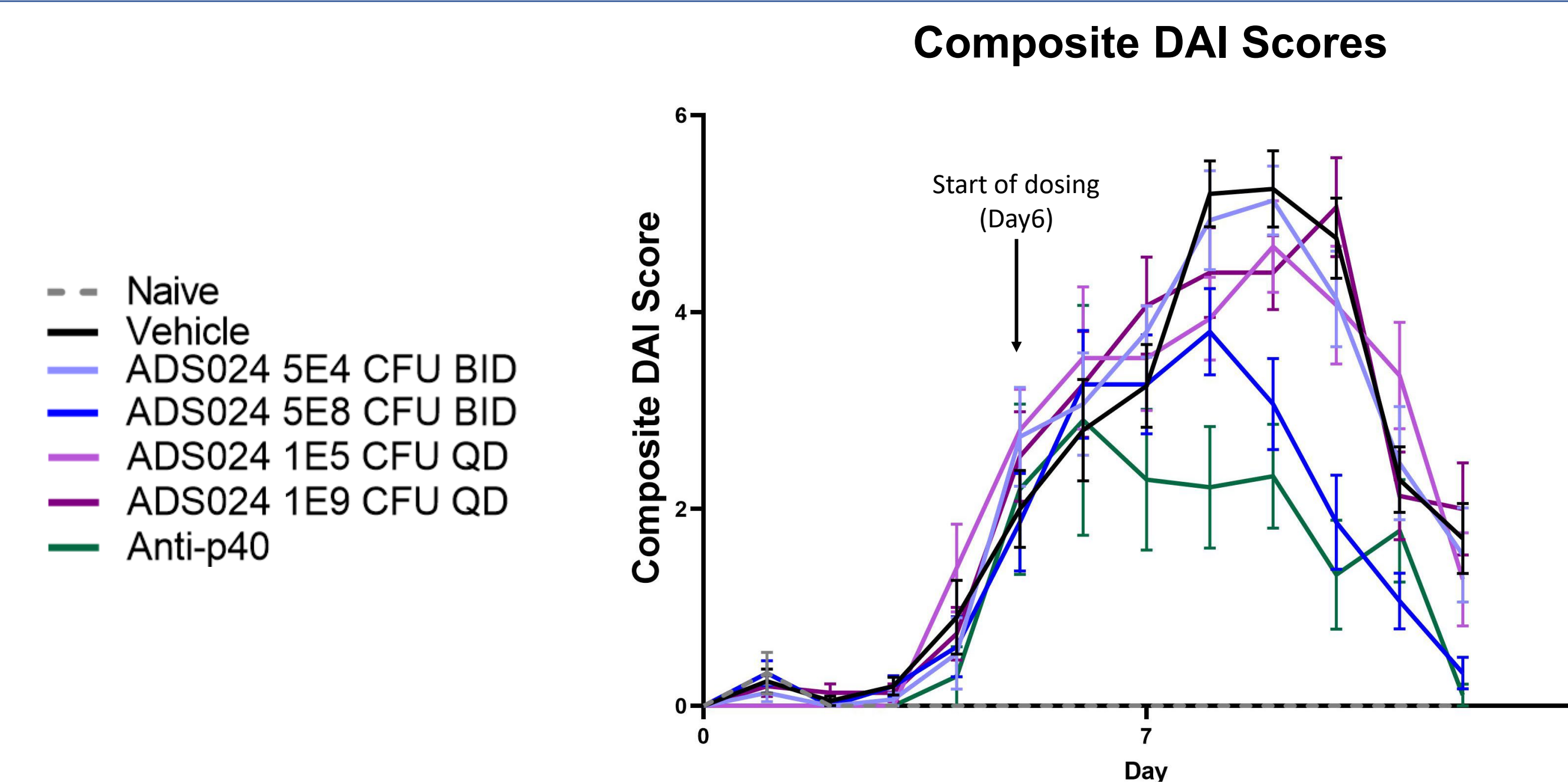


Fig 3. High dose ADS024 BID reduces colon weight/length ratio

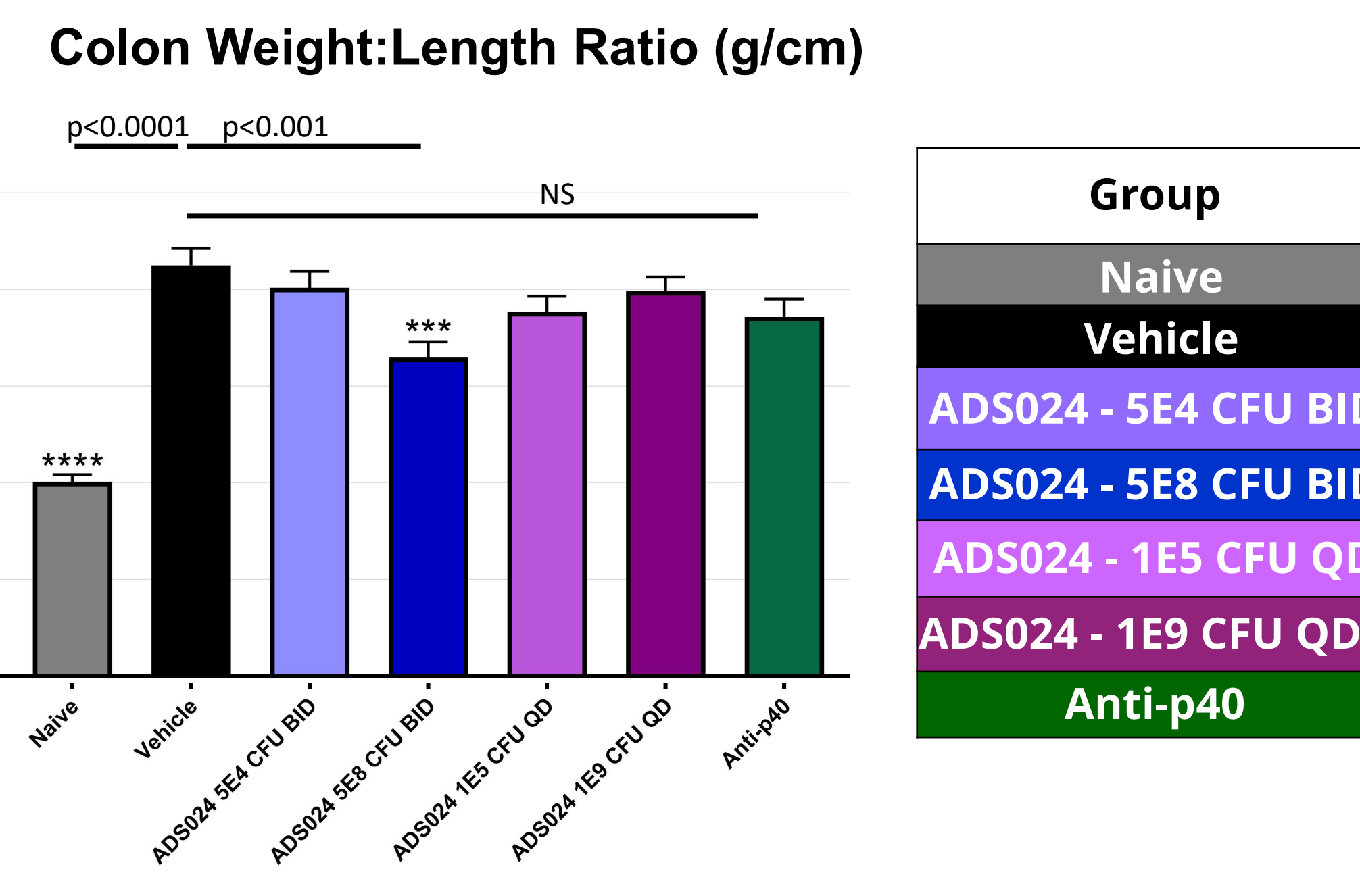


Fig 4. Impact of ADS024 on colonic cytokines and neutrophil marker MPO

