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Original research

Dose escalation randomised study of efmarodocokin alfa in healthy volunteers and patients with ulcerative colitis

Frank Wagner,[1] John C Mansfield ,[2] Annemarie N Lekkerkerker,[3] Yehong Wang,[3] Mary Keir,[3] Ajit Dash,[3] Brandon Butcher,[3] Brandon Harder ,[3] Luz D Orozco,[3] Jordan S Mar ,[3] Hao Chen,[3] Michael E Rothenberg [3]

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[1]Charité Research Organization, Berlin, Germany
[2]Gastroenterology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[3]Genentech Inc, South San Francisco, California, USA

Correspondence to
Dr Michael E Rothenberg, Genentech Inc, South San Francisco, CA 94080, USA; rothenberg.michael@gene.com

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ABSTRACT

Background The interleukin-22 cytokine (IL-22) has demonstrated efficacy in preclinical colitis models with non-immunosuppressive mechanism of action. Efmarodocokin alfa (UTTR1147A) is a fusion protein agonist that links IL-22 to the crystallisable fragment (Fc) of human IgG_4 for improved pharmacokinetic characteristics, but with a mutation to minimise Fc effector functions.

Methods This randomised, phase 1b study evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of repeat intravenous dosing of efmarodocokin alfa in healthy volunteers (HVs; n=32) and patients with ulcerative colitis (n=24) at 30–90 µg/kg doses given once every 2 weeks or monthly (every 4 weeks) for 12 weeks (6:2 active:placebo per cohort).

Results The most common adverse events (AEs) were on-target, reversible, dermatological effects (dry skin, erythema and pruritus). Dose-limiting non-serious dermatological AEs (severe dry skin, erythema, exfoliation and discomfort) were seen at 90 µg/kg once every 2 weeks (HVs, n=2; patients, n=1). Pharmacokinetics were generally dose-proportional across the dose levels, but patients demonstrated lower drug exposures relative to HVs at the same dose. IL-22 serum biomarkers and IL-22-responsive genes in colon biopsies were induced with active treatment, and microbiota composition changed consistent with a reversal in baseline dysbiosis. As a phase 1b study, efficacy endpoints were exploratory only. Clinical response was observed in 7/18 active-treated and 1/6 placebo-treated patients; clinical remission was observed in 5/18 active-treated and 0/6 placebo-treated patients.

Conclusion Efmarodocokin alfa had an adequate safety and pharmacokinetic profile in HVs and patients. Biomarker data confirmed IL-22R pathway activation in the colonic epithelium. Results support further investigation of this non-immunosuppressive potential inflammatory bowel disease therapeutic.

Trial registration number NCT02749630.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Many patients with moderate to severe ulcerative colitis do not achieve sustained remission, continue to require corticosteroid treatment and often develop treatment-related adverse effects—including infections—likely as a result of immune dysregulation induced by the approved therapies.

⇒ Efmarodocokin alfa (UTTR1147A), an investigational therapeutic expected to be non-immunosuppressive, is an agonist that activates the IL-22 signalling pathway in the colonic epithelium, where the IL-22R is expressed, to promote gut healing.

WHAT THIS STUDY ADDS

⇒ Efmarodocokin alfa had an adequate safety and pharmacokinetic profile in healthy volunteers and patients. Additionally, there was induction of colonic gene expression consistent with IL-22 activity in the intestinal epithelium, and treatment-specific effects on the gut microbiota in patients with ulcerative colitis resulting in improvements in dysbiosis. These preliminary findings need to be confirmed in subsequent trials.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The activity of efmarodocokin alfa on the intestinal epithelium and its non-immunosuppresive mechanism of action may provide benefit in the treatment of inflammatory bowel disease if subsequent studies show favourable safety and efficacy.

INTRODUCTION

Interleukin (IL)-22 is a cytokine with multiple roles in host defence and intestinal health.[1] The signalling pathway is involved in inflammation, cell proliferation and tissue regeneration, leading to therapeutic evaluation in different diseases, such as ulcerative colitis (UC). Its receptor, IL-22R, is expressed exclusively on epithelial tissues, including the gastrointestinal (GI) tract epithelium.[2] Microbial damage to the intestinal epithelium induces production of proinflammatory cytokines from myeloid cells, that in turn stimulate lymphocytes and innate lymphoid cells to secrete IL-22.[1] IL-22 regulates epithelial homeostasis and barrier function, upregulating

antimicrobial peptides, increasing mucin production and stimulating epithelial barrier repair.[1 3 4]

Efmarodocokin alfa (UTTR1147A) is a fusion protein consisting of IL-22 linked to the crystallisable fragment (Fc) portion of human immunoglobulin G4 to improve the cytokine's pharmacokinetic (PK) characteristics.[5] Efmarodocokin alfa activated the IL-22 pathway after intravenous administration in cynomolgus monkeys[5 6] as indicated by dose-dependent elevations in biomarkers of IL-22R signalling, including acute phase proteins (serum amyloid A (SAA); lipopolysaccharide binding protein; fibrinogen; C reactive protein (CRP))[7–9] and regenerating islet-derived protein 3 alpha (REG3A).[10–12] Intravenous and subcutaneous single ascending doses of efmarodocokin alfa tested in healthy volunteers (HVs) in a phase 1a trial demonstrated dose-dependent increases in serum levels of pharmacodynamic (PD) biomarkers: REG3A, CRP and SAA.[13] Most adverse events (AEs) were on-target dose-dependent and reversible effects in the skin reflective of IL-22R target engagement, and impacted tolerability at high doses. As of today, there are no approved IL-22 agonists, but various early phase studies of efmarodocokin alfa or other IL-22 agonists are ongoing or were recently completed in various diseases, including UC (this study), diabetic foot ulcer,[14] COVID-19 pneumonia,[15] graft-versus-host disease (NCT04539470; NCT02406651) and alcoholic hepatitis.[16] Here, we report results from a phase 1b multiple ascending dose study conducted to investigate the safety and tolerability, PK, PD and exploratory efficacy of efmarodocokin alfa in HVs and patients with moderate to severe UC.

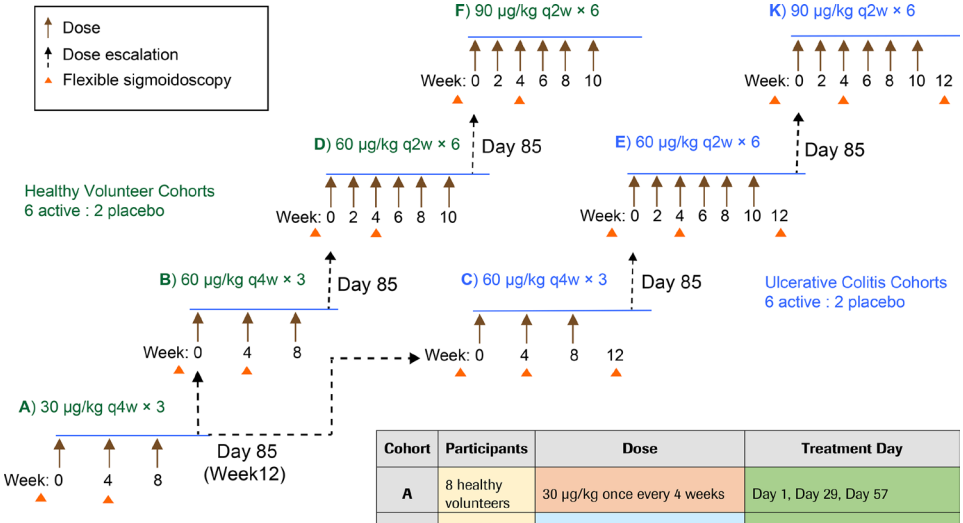
METHODS

Study design

This phase 1b multicentre, randomised, observer-blinded, placebo-controlled study (ClinicalTrials.gov: NCT02749630) evaluated the safety, tolerability, PK, immunogenicity and PD of repeat intravenous dosing of efmarodocokin alfa administered in HVs and patients with UC. Participants were enrolled at one site each in Germany and the UK starting April 2016 and ending February 2020 (online supplemental figure 1). HVs were enrolled into four dose-escalation cohorts: (A) 30 µg/kg every 4 weeks ×3 doses; (B) 60 µg/kg every 4 weeks ×3 doses; (D) 60 µg/kg every 2 weeks ×6 doses; (F) 90 µg/kg every 2 weeks ×6 doses. HVs were randomised at ~6:2 ratio (active: placebo) (figure 1). While unblinded data are not reviewed by the sponsor in blinded, randomised, controlled late stage trials, the sponsor was unblinded in this phase 1b trial because the safety data was reviewed per protocol on a continuous basis, cohort by cohort, by an Internal Monitoring Committee consisting of sponsor representatives, to enable accurate assessments about safety and tolerability to support robust decision-making around dose-escalation and safety monitoring. Safety and tolerability were confirmed in HVs followed to day 85 post-treatment before enrolment of patients with UC into three dose-escalation cohorts: (C) 60 µg/kg every 4 weeks ×3 doses; (E) 60 µg/kg every 2 weeks ×6 doses; (K) 90 µg/kg every 2 weeks ×6 doses. Patients were randomised at ~6:2 ratio (active: placebo). The follow-up period for HVs and patients lasted from the last dose until day 134 or the early termination visit. Randomisation, blinding and dose escalation are detailed in online supplemental methods.

Ethics

This study was conducted per the International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice and the Principles of the Declaration of Helsinki or the laws and regulations of the country where the research was conducted. The study complied with the requirements of the ICH E2A guideline. Studies conducted in the European Union/European Economic Area complied with the E.U. Clinical Trial Directive (2001/20/EC). The protocol was approved by an Institutional



Cohort	Participants	Dose	Treatment Day
A	8 healthy volunteers	30 µg/kg once every 4 weeks	Day 1, Day 29, Day 57
B	8 healthy volunteers	60 µg/kg once every 4 weeks	Day 1, Day 29, Day 57
C	8 patients with UC	60 µg/kg once every 4 weeks	Day 1, Day 29, Day 57
D	8 healthy volunteers	60 µg/kg once every 2 weeks	Day 1, Day 15, Day 29, Day 43, Day 57, Day 71
E	8 patients with UC	60 µg/kg once every 2 weeks	Day 1, Day 15, Day 29, Day 43, Day 57, Day 71
F	8 healthy volunteers	90 µg/kg once every 2 weeks	Day 1, Day 15, Day 29, Day 43, Day 57, Day 71
K	8 patients with UC	90 µg/kg once every 2 weeks	Day 1, Day 15, Day 29, Day 43, Day 57, Day 71

Figure 1 Study design. UC, ulcerative colitis.

Review Board (IRB). All participants provided written, informed consent. All authors had access to the study data, and reviewed/approved the final manuscript.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this study; a plain language summary (lay summary; layperson summary) of the results was made available to patients: https://forpatients.roche.com/en/trials/autoimmune-disorder/ulcerative-colitis/a-safety-study-of-intravenously-administered-uttr1147a-in-health.html

Participants

HVs aged 18–50 years old with body mass index (BMI) of 18–32 kg/m^2, weight between 40 and 120 kg, and who were in good health as defined by the protocol were eligible for enrollment. Patients with UC were eligible if they were between 18 and 80 years old and had moderate to severe disease with an inadequate response or intolerance to standard therapy with 5-aminosalicylic acid (5-ASA) drugs, immunosuppressives (eg, azathioprine, 6-mercaptopurine or methotrexate) and/or steroids. Permitted biologic therapies included anti-TNF drugs or vedolizumab; patients had to be on a stable dose or have discontinued their dose ≥6 weeks prior to study drug administration on day 1. A diagnosis of moderate to severe UC defined as a Mayo Endoscopic Subscore of ≥2 points by central reading at screening was required of all patients. There was no requirement to have a specific rectal bleeding (RB) or stool frequency score for this phase 1b study.

Patients were screened within 28 days prior to the first dose to assess eligibility and obtain pretreatment histologic and biomarker baseline samples; flexible sigmoidoscopies with biopsies were used to rule out cytomegalovirus (CMV) disease and document any dysplasia. Patients without a colonoscopy within the past year were required to undergo a colonoscopy in lieu of flexible sigmoidoscopy.

At time of screening, patients were required to have a disease duration of ≥12 weeks and those on high-dose corticosteroids were required to have the dose reduced to ≤20 mg/day of prednisone or prednisone-equivalent for at least 2 weeks prior to dosing with study drug on day 1. Patients on budesonide multimatrix (MMX) were required to have the dose reduced to ≤6 mg for at least 2 weeks prior to study drug administration on day 1. It was required that topical corticosteroids and topical 5-ASA preparations be withdrawn for at least 1 week prior to study drug administration on day 1. Patients who were on oral 5-ASA were required to be on a stable dose or discontinue for at least 4 weeks prior to study drug administration on day 1. Patients who were on immunosuppressants (azathioprine, methotrexate or 6-mercaptopurine) were required to be on a stable dose or have discontinued therapy for at least 4 weeks prior to study drug administration on day 1. Patients who were on antibiotics were required to have discontinued therapy for at least 4 weeks prior to screening endoscopic procedure. Approved biological therapy included TNF inhibitors and vedolizumab; patients were required to be on a stable dose or have discontinued their dose 6 weeks (TNF inhibitors) or at least 6 weeks (vedolizumab) prior to study drug administration on day 1.

Patients were required either to have undergone a colonoscopy within the past year or consented to undergo a colonoscopy in lieu of a flexible sigmoidoscopy at screening. This colonoscopy was intended to confirm the extent of disease (proctitis (rectum only); left-sided colitis (up to the splenic flexure); extensive colitis—beyond the splenic flexure but not involving the entire colon and pancolitis); remove any adenomatous polyps, and document evidence of surveillance for dysplasia for all patients with left-sided colitis of >12 years duration and total/extensive colitis of >8 years duration. Patients were required to have a diagnosis of moderate to severe UC defined as a Mayo Endoscopic Subscore of ≥2 points by central reading at screening.

Both HVs and UC patients were excluded if they had a history of psoriasis, psoriatic arthritis, atopic dermatitis requiring treatment within the past year, any eczematous skin disorders requiring treatment within the past year, rosacea or any other inflammatory skin disorders; history of any cancer; history of anaphylaxis, hypersensitivity or drug allergies; use of any non-biological investigational drug or participation in an investigational study of a non-biological within 30 days before the first dose (or within 5 half-lives of the investigational product) or use of a biologic investigational therapy or participation in an investigational study of a biologic within 90 days or 5 half-lives before the first dose.

Additionally, UC patients were excluded if they had conditions other than UC that could have required treatment with >20 mg/day of prednisone or prednisone-equivalent during the study; poorly controlled diabetes; history of primary sclerosing cholangitis; active anti-TNFa induced psoriasiform or eczematous lesions at screening; a requirement for hospitalisation during the study due to severity of UC; moderate to severe anaemia (haemoglobin <90 g/L); presence of an ileostomy or colostomy; total proctocolectomy with ileal pouch anal anastomosis; history of fungal, herpes, parasitic or other infections; or active tuberculosis.

Safety assessments

The primary objectives for this study were to evaluate the safety and tolerability of repeat dosing of intravenous efmarodocokin alfa compared with placebo in HVs and in patients with UC. Safety assessments included AEs, standard laboratory assessments, vital signs and ECG. AEs were classified as mild, moderate or severe for HVs, while AE severity for patients was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (V.4.0). Dermatological AEs for both HVs and patients were assessed by a protocol-defined scale as previously described[13] (online supplemental table 1). This scale was a combination of a Visual Analogue Scale (VAS), body surface area (BSA) and the need for topical/oral intervention with or without steroids. However, any event with a VAS tolerability score of >3 to ≤6 was considered moderate and a score of >6 was considered severe, irrespective of BSA involved or therapeutic intervention.

PK and immunogenicity assessments

The PK objective for this study was to characterise the PK profile and parameters derived from serum concentration-time profile following repeat dosing of efmarodocokin alfa in HVs and patients with UC. The immunogenicity objective was to evaluate the immune response to efmarodocokin alfa based on the incidence of antidrug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline using a tiered strategy (online supplemental methods).

Clinical activity assessments

The Mayo Clinic Score (MCS), modified MCS (mMCS) and partial MCS (pMCS) were assessed in patients as exploratory endpoints to determine the potential effect of efmarodocokin

Table 1 Demographics and baseline characteristics

Healthy volunteers	Pooled Placebo (n=8)	Cohort A 30 µg/kg every 4 weeks (n=6)	Cohort B 60 µg/kg every 4 weeks (n=6)	Cohort D 60 µg/kg every 2 weeks (n=6)	Cohort F 90 µg/kg every 2 weeks (n=6)	Pooled Active (n=24)
Age (years) Mean (SD)	38.8 (7.3)	33.5 (6.9)	37.2 (8.6)	37.3 (9.9)	42.3 (7.1)	37.6 (8.3)
Sex Male, n (%)	8 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
Ethnicity Not Hispanic or Latino, n (%)	8 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
Race White, n (%)	8 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
Weight (kg) Mean (SD)	81.1 (8.4)	80.4 (10.1)	81.8 (7.5)	87.5 (12.2)	84.5 (7.9)	83.5 (9.4)
BMI (kg/m^2) Mean (SD)	24.8 (1.0)	25.1 (2.3)	26.1 (1.5)	26.7 (3.7)	26.9 (2.3)	26.2 (2.5)
Patients with ulcerative colitis	**Pooled Placebo (n=6)**	**Cohort C 60 µg/kg every 4 weeks (n=6)**	**Cohort E 60 µg/kg every 2 weeks (n=6)**	**Cohort K 90 µg/kg every 2 weeks (n=6)**	**Pooled Active (n=18)**	
Age (years) Mean (SD)	40.2 (12.8)	40.5 (15.8)	39.5 (16.3)	44.7 (7.3)	41.6 (13.1)	
Sex Male, n (%)	3 (50.0)	5 (83.3)	3 (50.0)	6 (100.0)	14 (77.8)	
Ethnicity not Hispanic or Latino, n (%)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	18 (100.0)	
Race White, n (%)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	18 (100.0)	
Weight (kg) Mean (SD)	82.6 (26.4)	79.8 (13.5)	81.2 (18.2)	91.1 (17.1)	84.0 (16.2)	
BMI (kg/m^2) Mean (SD)	26.4 (4.7)	25.2 (4.0)	26.3 (4.2)	26.9 (4.0)	26.2 (3.9)	
Disease duration (years) Mean (SD)	7.9 (6.9)	6.3 (6.3)	8.8 (7.2)	10.7 (13.9)		
Endoscopic score	2.7 (0.5)	2.7 (0.5)	2.7 (0.5)	2.3 (0.5)		
Modified MCS	5.8 (2.0)	6.7 (0.8)	5.8 (1.5)	3.2 (1.5)		

BMI, body mass index; MCS, Mayo Clinic Score.

alfa on measures of UC disease activity (online supplemental methods). All endoscopy images were centrally read and reviewed using the Mayo Endoscopic Score and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) (online supplemental methods).

Disease activity was documented at screening and subsequent visits. Change in scores was assessed from baseline to week 4 and week 12. Clinical remission was defined as attaining mMCS ≤2, Mayo RB subscore of 0 and other Mayo subscores of ≤1. Clinical response was defined as meeting one of the following: (1) Having a ≥3 point decrease from baseline in mMCS and ≥1 point decrease from baseline in Mayo RB subscore or Mayo RB subscore of 0 or 1; (2) Achieving clinical remission.

Biomarker assessments: serum

Exploratory objectives for this study included peripheral blood PD response to efmarodocokin alfa in HVs and patients with UC. REG3A was measured centrally, and CRP locally, as previously described[13] and/or detailed in online supplemental methods.

Biomarker assessments: intestinal biopsies

To assess the effect of efmarodocokin alfa treatment on intestinal gene expression profiles and mucosal microbiota, biopsies from HVs were collected from the sigmoid colon at screening and on day 30. Biopsies from patients were collected at screening, day 30 and day 85 from the most inflamed region in the sigmoid colon, avoiding ulcer bed and necrotic tissue, with biopsy of the ulcer edge if ulcers were present. DNA and RNA were extracted in parallel from intestinal biopsies, and processed/analysed as described (online supplemental methods).

Biomarker assessments: stool

Faecal calprotectin was measured centrally. Stool samples were used to assess bacterial taxa in HVs versus patients, and the treatment-specific effects on bacterial taxa in both groups. Stool samples were collected at screening as well as on days 29, 43, 64, 85 and 134. Stool sample processing, DNA extraction, 16SV4 rRNA gene sequencing/processing and whole metagenome sequencing (WMS)/processing are detailed in online supplemental methods.

Statistical analysis

Due to the small size of this study, no formal statistical analysis was performed for safety. All participants who received at least one dose of efmarodocokin alfa were included in the safety-evaluable (SE) population, including HVs and patients with UC. PK, immunogenicity and PD analyses were based on patients in the SE population treated with efmarodocokin alfa who had available PK, ADA and PD biomarker data, respectively. All randomised participants who received at least one dose of study drug and had at least one

Table 2 Adverse events (AEs)

Healthy volunteers, n (%)	Pooled Placebo (n=8)	Cohort A* 30 µg/kg every 4 weeks (n=6)	Cohort B* 60 µg/kg every 4 weeks (n=6)	Cohort D† 60 µg/kg every 2 weeks (n=6)	Cohort F† 90 µg/kg every 2 weeks (n=6)	Pooled active (n=24)
Total no subjects with ≥1 AE	5 (62.5)	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	23 (95.8)
Total no of events	13	23	37	37	40	137
Total no subjects withdrawn from study due to an AE	0	0	0	0	2 (33.3)	2 (8.3)
Total no subject with ≥1						
Serious AE	0	1 (16.7)	0	0	0	1 (4.2)
AE leading to withdrawal from treatment	0	0	1 (16.7)	0	2 (33.3)	3 (12.5)
Most common AEs in ≥2 of all participants						
Dermatological AEs						
Dry skin	1 (12.5)	3 (50.0)	6 (100.0)	5 (83.3)	6 (100.0)	20 (83.3)
Lip dry	0	3 (50.0)	3 (50.0)	6 (100.0)	5 (83.3)	17 (70.8)
Erythema	0	2 (33.3)	1 (16.7)	4 (66.7)	4 (66.7)	11 (45.8)
Skin exfoliation	0	1 (16.7)	1 (16.7)	3 (50.0)	4 (66.7)	9 (37.5)
Skin discomfort	0	0	1 (16.7)	3 (50.0)	4 (66.7)	8 (33.3)
Skin burning sensation	0	0	0	2 (33.3)	2 (33.3)	4 (16.7)
Other AEs						
Nasopharyngitis	3 (37.5)	3 (50.0)	3 (50.0)	5 (83.3)	1 (16.7)	12 (50.0)
Headache	2 (25.0)	0	2 (33.3)	0	1 (16.7)	3 (12.5)
Oropharyngeal pain	1 (12.5)	1 (16.7)	1 (16.7)	0	1 (16.7)	3 (12.5)

Patients with ulcerative colitis, n (%)	Pooled Placebo (n=6)	Cohort C* 60 µg/kg every 4 weeks (n=6)	Cohort E† 60 µg/kg every 2 weeks (n=6)	Cohort K† 90 µg/kg every 2 weeks (n=6)	Pooled active (n=18)
Total no subjects with ≥1 AE	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	18 (100.0)
Total no of events	63	61	63	53	177
Total no subjects withdrawn from study due to an AE	0	0	0	1 (16.7)	1 (5.6)
Total no subject with ≥1					
Serious AE	0	0	1 (16.7)	0	1 (5.6)
AE leading to withdrawal from treatment	0	0	0	1 (16.7)	1 (5.6)
Most common AEs in ≥2 of all participants					
Dermatological AEs					
Dry skin	2 (33.3)	5 (83.3)	4 (66.7)	6 (100.0)	15 (83.3)
Lip dry	1 (16.7)	4 (66.7)	4 (66.7)	5 (83.3)	13 (72.2)
Erythema	2 (33.3)	2 (33.3)	1 (16.7)	5 (83.3)	8 (44.4)
Pruritus	0	3 (50.0)	3 (50.0)	1 (16.7)	7 (38.9)
Skin discomfort	1 (16.7)	1 (16.7)	0	5 (83.3)	6 (33.3)
Skin exfoliation	1 (16.7)	0	2 (33.3)	0	2 (11.1)
Rash	1 (16.7)	1 (16.7)	1 (16.7)	0	2 (11.1)
Other AEs					
Nasopharyngitis	3 (50.0)	4 (66.7)	4 (66.7)	5 (83.3)	13 (72.2)
Headache	3 (50.0)	2 (33.3)	2 (33.3)	2 (33.3)	6 (33.3)
Diarrhoea	0	1 (16.7)	2 (33.3)	1 (16.7)	4 (22.2)
Abdominal pain	1 (16.7)	2 (33.3)	1 (16.7)	0	3 (16.7)
Oropharyngeal pain	1 (16.7)	0	2 (33.3)	1 (16.7)	3 (16.7)
Flatulence	0	1 (16.7)	2 (33.3)	0	3 (16.7)
Fever	0	0	2 (33.3)	1 (16.7)	3 (16.7)

*Cohorts A, B and C received three doses.
†Cohorts D, E, F and K received six doses.

post-baseline efficacy data point were included in the modified intent-to-treat population for activity analyses.

The sample size for this trial was based on dose-escalation rules, and not based on any statistical criteria. A sufficient number of subjects were screened to ensure approximately eight subjects in each HV cohort, and eight subjects in each UC cohort (6:2 efmarodocokin alfa:placebo).

RESULTS

Participants and baseline characteristics

The HV cohorts had white males with an average age of 37.9 years (range 23–51); the median weight and BMI were similar between cohorts (table 1). All patients with UC were white, predominantly male (70.8%), aged 41.2 years (range 26–71) (table 1). Patients had an average disease duration of 8.4 years

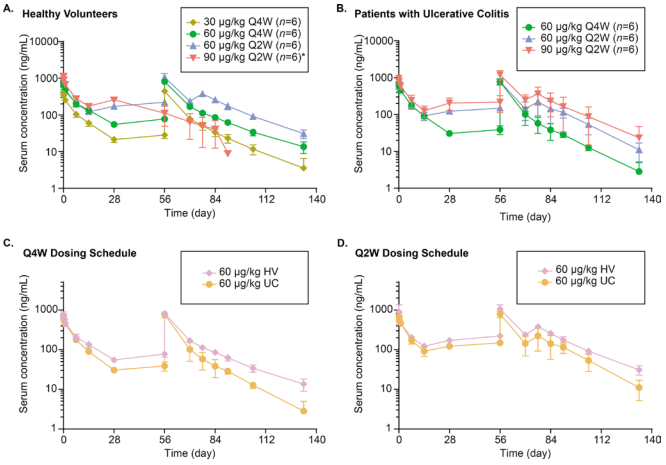


Figure 2 Pharmacokinetics (PK) of efmarodocokin alfa. PK in (A) all HV cohorts and (B) all UC patient cohorts. PK comparisons between HV and UC patients dosed at 60 µg/kg, given (C) once every 4 weeks and (D) once every 2 weeks. *Cohort F, 90 ug/kg every 2 weeks in HV, was discontinued either after the second dose (n=3) or third dose (n=3) due to dermatological dose-limiting adverse events (DLAEs). HV, healthy volunteers; UC, ulcerative colitis.

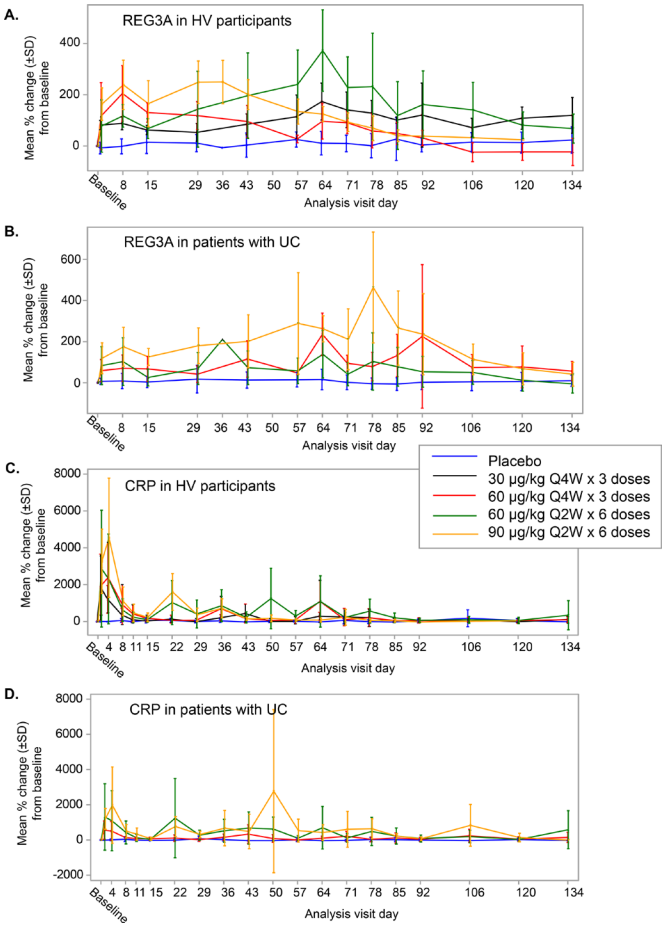


Figure 3 Serum biomarker response to efmarodocokin alfa. Percent change from baseline over time in serum REG3A levels in (A) HVs and (B) patients with UC and in serum CRP levels in (C) HVs and (D) patients with UC. Cohort F, 90 ug/ kg Q2W in HV, was discontinued either after the second dose (n=3) or third dose (n=3) due to dermatological dose-limiting adverse events (DLAE). CRP, C reactive protein; HVs, healthy volunteers; UC, ulcerative colitis.

at baseline (range 0.4–37.8) and all were on at least one disease-related concomitant treatment at baseline (online supplemental table 2). The majority of patients (20 of 24) were treatment-naïve to biologics at baseline with the exception of one patient (cohort E) on infliximab treatment that was ongoing, and three patients on vedolizumab treatment among whom one discontinued vedolizumab before entering the study. Seven of 18 (38.9%) patients who received efmarodocokin alfa were on prednisolone treatment at baseline that was continued at ≤10 mg during the study. The disease severity for all patients was indicated by average baseline scores for MCS (7.50, range 3.0–11.0), mMCS (5.38, range 2.0–8.0), pMCS (4.92, range 1.0–8.0), Mayo endoscopic subscore (2.58, range 2.0–3.0) and UCEIS (4.04, range 2.0–6.0).

Safety

All 56 participants in the study received at least one dose of study treatment (efmarodocokin alfa or placebo). Forty participants received all planned doses, including 23 of 32 HVs (71.9%) and 17 of 24 patients (70.8%). There were no treatment-related serious AEs, deaths or life-threatening AEs in either HVs or patients (online supplemental figure 1).

Twenty-eight HVs (87.5%) reported at least one AE among 23 of 24 who received efmarodocokin alfa (95.8%) and 5 of 8 (62.5%) who received placebo (online supplemental table 3). Overall, the most common AEs in HVs were nasopharyngitis, and expected on-target effects including dry skin, dry lip, erythema and skin exfoliation (table 2). Skin-related AEs seen with active treatment (21 of 24) vs placebo (1 of 8) occurred more frequently at doses of 60 µg/kg or higher (cohorts B, D and F) (online supplemental table 4). The VAS component of the skin-related severity scale (online supplemental table 1) by itself was enough to categorise moderate and severe events independent of BSA and intervention, and likely led to upgrading the severity of skin-related AEs.

All 24 patients with UC (100%) reported AEs (online supplemental tables 2 and 3). Overall, the most common AEs by preferred term reported in patients with UC were dry skin, dry lip, nasopharyngitis, erythema and pruritus (table 2). Skin-related AEs were reported in 83%–100% of patients who received active treatment in cohorts C, E and K compared with 50% of placebo-treated patients (online supplemental table 4).

A total of 7 dermatologic effects (dose-limiting adverse events, DLAEs) occurred in 2 (33.3%) HVs (cohort F; 3 AEs each) and 1 (16.7%) patient (cohort K; 1 AE)—all had received efmarodocokin alfa at 90 µg/kg every 2 weeks. The MTD was determined to be 60 µg/kg every 2 weeks for HVs and was not determined for UC patients since no dosing regimen administered to patients met protocol-defined criteria for a non-tolerated dose. No clear trends emerged in ECG intervals, vital signs and other labs (online supplemental table 5) in HVs or patients except for serum CRP (considered a PD biomarker; details under 'PD' below) and fibrinogen increases (considered a safety lab). Fibrinogen increases were seen in both active and placebo treatments (HV 58.1% including 1/8 placebo and 17/23 active; patients 72.2% including 1/5 placebo and 12/13 active) (online supplemental figure 2). Other safety details are available in online supplemental materials.

Pharmacokinetics

In both HVs and patients with UC, efmarodocokin alfa exposures were approximately dose proportional (figure 2). In HVs, the $t_{1/2}$ was 15.7–17.7 days across cohorts, and in patients, the

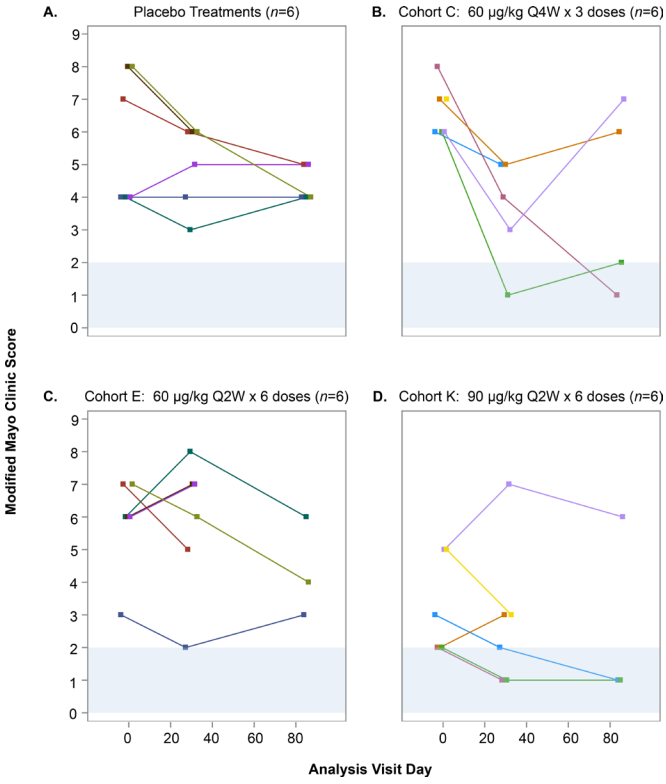


Figure 4 Patient plots of modified Mayo Clinic Score (mMCS) at baseline, week 4 and week 12 in the (A) placebo cohort; (B) cohort C; (C) cohort E and (D) cohort K.

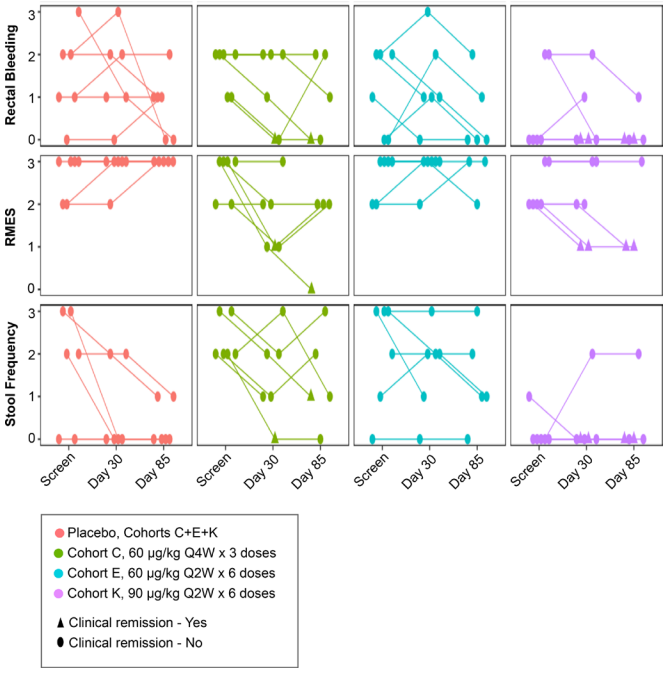


Figure 5 Effects of efmarodocokin alfa on stool frequency, Robarts Mayo Endoscopic Score (RMES) and rectal bleeding in different dose cohorts. Scores here were part of the modified Mayo Clinic Score presented in figure 4.

$t_{1/2}$ was 12.4–13.8 days across cohorts (online supplemental table 6). Although C_{max} values were comparable between HVs and patients, patients had relatively lower exposures than HVs as reflected by C_{trough} and area under the curve (AUC) values. For the 60 µg/kg every 4 weeks regimen, group mean trough concentrations after first and last doses, $C_{trough,\ D28}$ and $C_{trough,\ SS}$, were 30.5 and 38.2 ng/mL, respectively, approximately 42%–45% of HV exposures. AUC values for the first and last dose intervals ($AUC_{D0\text{-}28}$, $AUC_{D56\text{-}84}$) in patients were approximately 80% of those from HVs.

Immunogenicity

The baseline prevalence of ADAs in HVs was 1 in 32 (3.1%; cohort F) and 1 in 24 (4.2%; cohort K) for patients with UC. There were no treatment-emergent ADAs in this study.

Pharmacodynamics

Efmarodocokin alfa treatment resulted in the elevation of IL-22 serum biomarkers REG3A and CRP, consistent with IL-22 pharmacology and indicative of on-target IL-22R engagement, as seen previously.[5 6 13] These changes were not observed with placebo treatment in HVs or patients (figure 3). Dose-dependent trends for REG3A and CRP (figure 3) in HVs and patients were most apparent after the first dose across all active treatment dose groups, likely due to the increased time (7–14 days) between dosing and sampling at later doses that impacted the levels detected. HVs receiving the 90 µg/kg every 2 weeks regimen were discontinued either after the second (n=3) or third dose (n=3). As a result, the effect of active treatment on PD biomarker data after day 29 cannot be analysed for this cohort.

No overall effect of efmarodocokin alfa on faecal calprotectin, a biomarker of intestinal inflammation,[17] was detected among HVs. For most patients, baseline faecal calprotectin levels were in the active disease range; with one of eight patients in each of cohort C, E and K having baseline levels below 250 µg/g, indicating lower disease activity at baseline. Overall, patients showed similar reductions in faecal calprotectin with efmarodocokin alfa treatment as with placebo (online supplemental figure 3).

Clinical remission and response in patients with UC

The MCS, pMCS and mMCS were assessed at baseline, week 4 (day 30) and week 12 (day 85) as exploratory endpoints. The baseline mean mMCS score was 5.83 among placebo-treated patients, and 6.67, 5.83 and 3.17 across cohorts C, E and K, respectively, treated with efmarodocokin alfa. Overall, the mMCS decreased over time in active-treated cohorts (figures 4 and 5). Data for weeks 4 and 12 mMCS, MCS and pMCS (median, range and change from baseline) are shown in online supplemental table 7. Data for histological scores in patients as measured by Geboes score,[18] Nancy index[19 20] and Robarts histologic index[21] at baseline and following treatment with efmarodocokin alfa are shown in figure 6. No clear effect was demonstrated with regard to endoscopy (figure 5) or histology (figure 6). Response data are provided in detail in online supplemental materials.

Clinical remission was observed in 5 out of 18 patients treated with efmarodocokin alfa (cohort C, n=2; cohort K, n=3) compared with 0 of 6 placebo-treated patients. Among these, three had achieved clinical remission by week 4 (day 28) (online supplemental table 8). Clinical response was achieved in 7 out of 18 patients treated with efmarodocokin alfa (cohort C, n=3; cohort E, n=1; cohort K, n=3) compared with 1 of 6 placebo-treated patients. Endoscopy remission and healing were measured with UCEIS scores (online supplemental figure 4) and mean centrally read endoscopic scores (online supplemental figure 5). One of 18 patients achieved endoscopic remission and 6 of 18 achieved endoscopic healing (online supplemental table

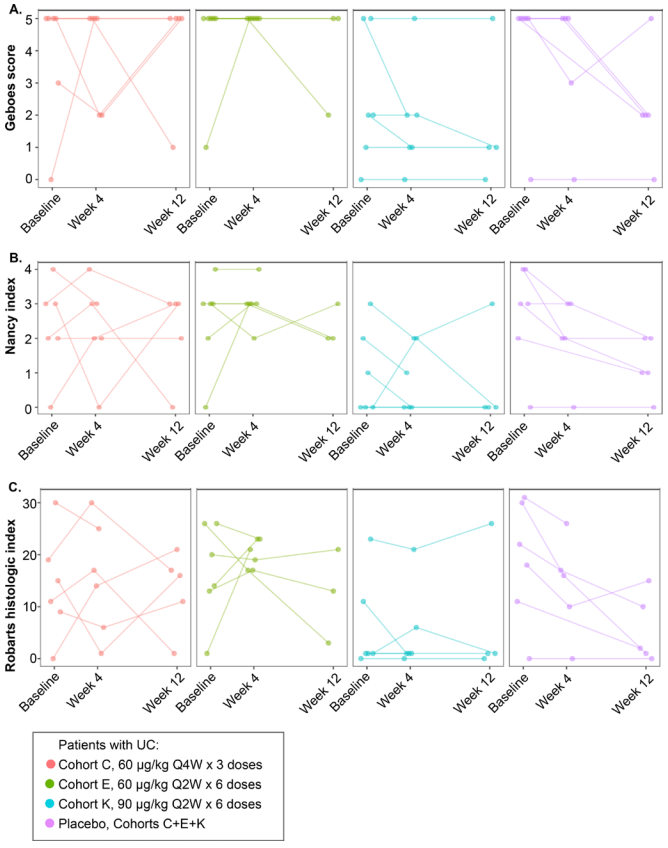


Figure 6 Histological scores in patients with ulcerative colitis at baseline and following treatment with efmarodocokin alfa as measured by (A) Geboes Score; (B) Nancy Index (C) Robarts Histologic Index. UC, ulcerative colitis.

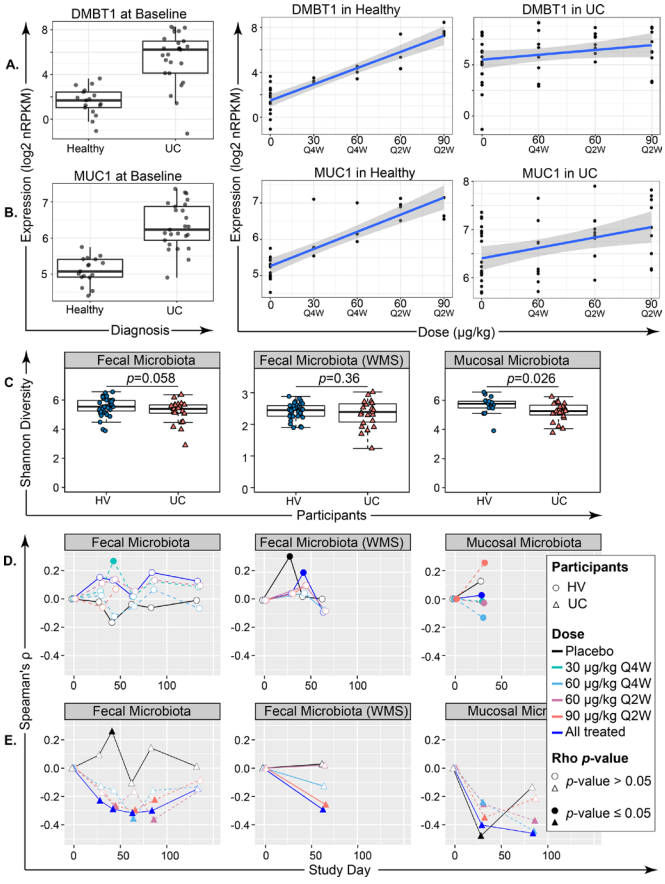


Figure 7 Effects of efmarodocokin alfa on gene expression and microbiota. Expression of IL-22 signature genes (A) *DMBT1* and (B) *MUC1* in the colon of HV and patients. Expression is shown at baseline, and after efmarodocokin alfa treatments. Each sample point is a donor, and the y-axis shows normalised expression values from bulk RNAseq as log2(nRPKM). (C) Shannon Diversity for the microbiota of HV and patients with UC at baseline before administration of study drug. (D) The Spearman correlation coefficient (ρ) for Log_2 FC in abundance from baseline (treatment effect) in HV vs Log_2 FC in abundance between UC and HV at baseline (dysbiosis effect). (E) Spearman correlation coefficient (ρ) of treatment effect in patients with UC vs dysbiosis effect. For C–E, faecal microbiota (16S rRNA gene sequencing), faecal microbiota (WMS) and mucosal microbiota (16S rRNA gene sequencing) are depicted. For C, p value was determined by t-test. Note that data from study days >43 in the HV cohort receiving the 90 µg/kg every 2 weeks dosing regimen were omitted due to early termination. HV, healthy volunteers; UC, ulcerative colitis; WMS, whole metagenome sequencing.

8). However, given the small sample size, between-patient variability and exploratory nature of these endpoints, no conclusion about efficacy can be made from these data. A well-controlled and adequately powered randomised controlled trial would be required to establish efficacy.

RB and SF scores trended down for active as well as placebo treatment cohorts (online supplemental table 7). At baseline, the median RB scores were 1.5 for placebo, and 2.0, 1.5 and 0.0 for cohorts C, E and K, respectively; the median change from baseline at week 12 were −0.5 for placebo, and −1.0, 0.0 and 0.0 for cohorts C, E and K respectively. At baseline, the median SF scores were 2.0 for placebo, and 2.0, 2.5 and 0.0 for cohorts C, E and K, respectively; the median change from baseline at week 12 were −1.5 for placebo, and −1.0, 0.0 and 0.0 for cohorts C, E and K, respectively.

Il-22 inducible gene expression

IL-22 inducible epithelial genes *DMBT1* and *MUC1*,[3 22] which were identified through meta-analysis of expression profiles of IL-22 stimulated human colonoids[23] (manuscript in preparation), were evaluated at baseline vs post-treatment timepoints in HVs and patients. Treatment with efmarodocokin alfa resulted in dose-related induction of *DMBT1*[22] and *MUC1*[3] in HVs and patients (figure 7A,B), indicative of IL-22R engagement in the tissue and demonstrating trends of higher induction of expression in the higher dose cohorts, but was less pronounced in patients versus HVs. Patients with UC are known to have elevated levels of IL-22 in circulation,[24] suggesting potential increased IL-22 activation in the colon at baseline. Indeed, we observed higher expression of *MUC1* and *DMBT1* in patients compared with HVs at baseline, and hence a smaller net difference on induction with efmarodocokin alfa in patients (figure 7A,B).

Additionally, in line with induction of STAT3-signalling, treatment with efmarodocokin resulted in induction of *STAT3*, *MUC4*, *REG1A* and *REG3A* (online supplemental figure 6).

Microbiota PD results

Consistent with previous studies,[25] reduced Shannon's diversity was observed in baseline stool and biopsies from UC patients versus HVs, indicating a level of broad microbial dysbiosis in patients (figure 7C). Microbial diversity did not significantly change post-treatment versus baseline, regardless of participant health status and efmarodocokin alfa dosing regimen (online

supplemental figures 7 and 8). Trends of increased diversity in cohorts with higher drug concentrations and more frequent dosing (60 µg/kg every 2 weeks and 90 µg/kg every 2 weeks) were observed over time, but this increase only approached statistical significance in the faecal microbiota of HV in the 60 µg/kg every 2 weeks dosing group at day 43 (online supplemental figure 7A), faecal microbiota p=0.054, faecal microbiota (whole metagenome sequencing (WMS)) p=0.10.

The relative abundances of bacterial genera were evaluated for treatment-specific effects in relation to UC-dysbiosis. A dysbiosis effect for each genus was calculated by comparing its mean baseline abundance in patients vs HV. Similarly, a treatment effect for each genus was calculated by comparing its mean abundance at a given study day to its mean abundance at baseline for each study cohort (see the Methods section). This enabled evaluation of the effect of dosing on general UC-dysbiosis. In HV cohorts, the Spearman's correlation coefficient (ρ) for treatment effect compared with dysbiosis effect was statistically significant ($p<0.05$) at a minority of time points and predominantly ranged from −0.2 to 0.2 at all time points regardless of dosing cohort, microbiota location and sequencing technology (figure 7D). Conversely, treatment effect correlated consistently negatively with dysbiosis effect across UC cohorts, sampling location and microbiota profiling technology, with statistically significant spearman's correlation coefficients (ρ) exceeding −0.2 at a majority of timepoints in active-treated cohorts and only once in placebo-treated patients (figure 7E). This suggests changes in microbiota composition following efmarodocokin alfa exposure are counter to the dysbiosis found in patients. Furthermore, at study day 85 (the first microbiota sample collected after all dosing regimens were complete), treatment effect still correlated negatively with dysbiosis effect in all treated UC-cohorts (individually and combined) in both the faecal and mucosal microbiota (online supplemental figure 9), suggesting effects on microbiota composition persist following cessation of treatment. Combined, these observations suggest efmarodocokin alfa treatment is accompanied by changes in microbiota composition that may counter features of UC-dysbiosis.

DISCUSSION

Although several agents are approved for the treatment of UC, the unmet medical need remains high.[26] Efmarodocokin alfa is an agonist that activates the IL-22 signalling pathway through IL-22R, expressed on the colonic epithelium, to promote healing without acting directly on haematopoietic cells. This phase 1b study demonstrated an adequate safety, tolerability and PK profile in HVs and patients with moderate to severe UC on repeat intravenous dosing with efmarodocokin alfa versus placebo, with induction of colonic gene expression consistent with IL-22 activity in the intestinal epithelium, and treatment-specific effects on the gut microbiota in patients resulting in improvements in UC dysbiosis. None of the study participants developed any ADA to efmarodocokin alfa, suggesting that the potential for immunogenicity is low.

Given the nature of efmarodocokin alfa as an agonist and the DLAEs that were seen in HVs in the phase 1a trial, dose selection in phase 1b was challenging. In the phase 1a trial,[13] even 50% increases in exposure from 60 µg/kg to 90 µg/kg resulted in very different tolerability profiles in HVs. The starting dose of 30 µg/kg every 4 weeks was selected because a clear trend of REG3A upregulation at this level was observed in the phase 1a trial. PK/PD and tolerability in HV cohorts supported ungating the patient cohorts at the same dose level. Interestingly, it was observed that patients had relatively lower drug exposures in comparison to HVs when dosed at the same dose level. The lower exposure is consistent with better tolerability in the patient population. Patients with UC generally tolerated the highest dose administered, 90 µg/kg every 2 weeks, as only one patient developed a DLAE; thus, an MTD was not defined for patients. However, dosing at 90 µg/kg every 2 weeks was stopped in HVs due to intolerable DLAEs occurring in several participants; 90 µg/kg every 2 weeks was therefore above the MTD in HVs. The attrition rate generated in this study is one parameter among several others to be taken into consideration for powering large phase 2 studies and beyond.[27 28] Interestingly, differences in PK for different populations (eg, HVs vs inflammatory bowel disease, patients witth IBD) is not unique to efmarodocokin alfa, and has been seen with anrukinzumab[29] and infliximab.[30] There are several possible underlying causes that could impact clearance of biologics in IBD, including differences in GI permeability that leads to losses into the lumen, increased catabolism due to the inflammatory state or other differences.[24 31]

Patients with UC are at increased risk for colon cancer,[32] likely as a result of the tumourigenic effects of chronic inflammation on the colonic epithelium.[33 34] IL-22 may have a protective role in promoting gut homeostasis, but may also promote tumourigenesis[35 36] although further investigation is needed.[37] Therefore, while efmarodocokin alfa could potentially decrease rates of colon cancer by promoting epithelial healing (if this is demonstrated in subsequent clinical trials), one of the on-target potential risks for this growth factor may well be the promotion of tumours that express IL-22R. Although no evidence of tumourigenesis or tumour growth promotion resulting from efmarodocokin alfa therapy was evident in the current and prior studies,[5 6 13] it remains unknown whether efmarodocokin alfa could potentially promote tumour progression in patients with chronic administration.

The pharmacological activity and IL-22 pathway activation by efmarodocokin alfa was supported by observed PD effects in serum, stool and tissue. Serum measurements of REG3A levels showed treatment-dependent increases, confirming previous observations.[5 6 13] Increases in CRP levels were also observed, without signs or symptoms of inflammation (fever, tachycardia, hypotension, headache or changes in vital signs), consistent with observations described previously.[13 38] CRP is a biomarker of inflammation and is not itself proinflammatory,[38] so this drug-induced increase on CRP is not expected to adversely impact inflammation in UC. Observed normalised mean peak levels of REG3A and CRP appeared lower for patient dose cohorts, likely due to the relatively lower drug exposures in patients versus HVs, indicated by same dose level PK parameters.

IL-22 has been shown to have effects on the microbiota as well as on the epithelial barrier.[1] Murine studies have shown that mice deficient in IL-22 or *Il22ra1* have exacerbated colitis,[39] while treatment with IL-22 cytokine or IL-22Fc fusion protein is protective[5 40] and also limits intestinal permeability.[41] Consistent with previous studies, we found that patients with UC have decreased faecal and mucosal bacterial diversity in comparison to HVs. Overall measures of bacterial diversity trended upwards in patients following treatment with efmarodocokin alfa, particularly in the highest dose groups. IL-22 has been shown to have effects on molecules involved in host-microbe interactions, including mucin production,[3] fucosylation[42] and antimicrobial protein production,[43] all of which may impact microbial diversity. An analysis of bacterial taxa that were differentially abundant at baseline between the HV and UC cohorts showed significant depletion of UC-associated bacterial taxa and enrichment of

HV-associated bacterial taxa following treatment that persisted in higher dose groups out to day 85. Others have similarly shown that anti-TNF, anti-integrin and faecal microbiota transplant treatment all allow partial restoration of intestinal microbiota in IBD patients, particularly those achieving clinical response.[44 45] It is unclear whether these effects are driven by resolution of inflammation, specific effects on microbes, changes in host gene expression and/or barrier function.

Analysis of biopsy samples from HVs and patients for gene expression of *DMBT1*,[22] an antimicrobial protein and *MUC1*,[3] involved in mucus production, showed dose-related increases following efmarodocokin alfa treatment. *DMBT1* and *MUC1*are signature genes indicative of IL-22R engagement in the colon (manuscript in preparation) and demonstrate a PD effect of efmarodocokin alfa. Expression of these signature genes was higher in patients versus HVs, likely due to elevated baseline levels of IL-22 in patients with UC[24] leading to a smaller net change with efmarodocokin alfa treatment.

While the enrolled patient population had active endoscopic disease as well as ongoing UC symptoms of RB and increased stool frequency, the inclusion criteria for this phase 1b study required endoscopic activity only (Mayo endoscopic subscore of 2 or higher), which was considered a key factor for determining PK in patients with UC. Endoscopic activity would also most reliably characterise any exploratory activity/efficacy of the drug, thereby guiding subsequent decision making about clinical development. Regarding exploratory efficacy, the observed MCS, mMCS and pMCS scores decreased over time in all cohorts, and a larger percentage of patients appear to have achieved clinical response and clinical remission on efmarodocokin alfa compared with placebo. However, due to the small sample size, the large between-patient variability, the small numbers of responders and remitters, the exploratory nature of this phase 1b study (which was not intended or powered to show efficacy), the largely biological-naïve study population (which is subject to larger placebo responses than more refractory UC populations), and the lack of a dose relationship with regard to the exploratory efficacy endpoints, there is no conclusion regarding any potential therapeutic effect of efmarodocokin alfa. Furthermore, there was no clear effect with regard to centrally-read endoscopic healing, endoscopic remission or histology scores. The lack of a clear effect and the apparent disconnect between endoscopy and histology could be due to several possible reasons: First, this study was not designed or powered to show a difference from placebo on these endpoints. Second, endoscopy and histology endpoints may not always correlate perfectly, particularly in a small, exploratory study.[46] Third, the dose or dosing interval of efmarodocokin alfa may not be optimised at this early stage of development to achieve a maximal effect. Fourth, the narrow therapeutic index of this systemically administered drug may have prevented testing of higher doses. Fifth, the effect of efmarodocokin alfa on the colonic mucosa may be small or transient. And lastly, only a subset of patients might benefit. Future well-controlled and adequately powered trials intended to explore the potential for benefit on clinical readouts such as endoscopy, patient-reported outcomes such as stool frequency and RB, or histology are needed to further explore potential efficacy.

Patients in clinical remission/response appeared to have skin AEs comparable to non-remitters and non-responders. Across all active UC cohorts, 5/5 patients who achieved clinical remission had a skin AE, whereas 12/13 patients who did not achieve clinical remission had a skin AE. Although this study could not definitively show the safety or efficacy of efmarodocokin alfa in combination with other treatments of UC, one patient had concomitant treatment with infliximab and two others were treated with stable doses of vedolizumab. There were no safety concerns observed as a result of concomitant treatment with infliximab or vedolizumab.

In conclusion, this phase 1b study of efmarodocokin alfa in HVs and patients with UC demonstrated adequate safety and PK of multiple doses while confirming the evidence for IL-22R engagement and dose-dependent pharmacological activity.

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Patient consent for publication Not applicable.

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ORCID iDs
John C Mansfield http://orcid.org/0000-0003-2490-7750
Brandon Harder http://orcid.org/0000-0002-2555-7038
Jordan S Mar http://orcid.org/0000-0002-0060-802X
Michael E Rothenberg http://orcid.org/0000-0002-4603-6653

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