



Randomised clinical trial: a phase 1b study of GB004, an oral HIF-1 α stabiliser, for treatment of ulcerative colitis

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Summary

Background: Epithelial barrier dysfunction contributes to a dysregulated intestinal immune response in ulcerative colitis (UC). GB004 is an orally administered, small molecule, gut-targeted stabiliser of hypoxia-inducible factor-1 α , a transcription factor with protective roles at the epithelial layer of the inflamed gut.

Aims: To evaluate safety, pharmacokinetics, pharmacodynamics and efficacy of GB004 in patients with active UC.

Methods: This double-blind, placebo-controlled study randomised patients 2:1 to receive an oral solution of GB004 120 mg or placebo once daily for 28 days. Eligible patients had a Robarts Histopathology Index score ≥ 4 with neutrophils in the epithelium, total Mayo Clinic score 3-12, Mayo Clinic endoscopic subscore ≥ 1 , and blood in the stool, despite treatment with 5-aminosalicylates, corticosteroids or immunosuppressants.

Results: Thirty-four patients were randomised. GB004 120 mg for 28 days was generally well-tolerated. Adverse events occurred in 27.3% (3/11) and 39.1% (9/23) of patients in the placebo and GB004 groups respectively. Nausea and dysgeusia were most commonly reported in the GB004 group (0% for placebo and 21.7% [5/23] and 13.0% [3/23] respectively for GB004). There were no treatment-related serious adverse events or deaths. GB004 exhibited minimal accumulation, with higher colonic concentrations relative to plasma. Exploratory pharmacodynamic and efficacy analyses demonstrated GB004 target engagement and numerically higher proportions of patients achieving improvement in multiple measures of disease activity, respectively, at day 28 for GB004 compared to placebo.

Conclusion: Results from this phase 1b trial support evaluation of the full therapeutic potential of GB004 for the treatment of UC. A phase 2 study (NCT04556383) is ongoing. *Clinicaltrials.gov* NCT03860896.

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1 | INTRODUCTION

Chronic recurrent inflammation is a hallmark of the inflammatory bowel disease, ulcerative colitis (UC).¹ Critical components of UC disease pathophysiology include epithelial barrier dysfunction and increased intestinal permeability that result in the exposure of the intestinal immune system to luminal flora and antigens and contribute to a dysregulated intestinal immune response.^{2,3} Given the well-described relationship between sustained immune responses and chronic inflammation, therapies have been employed that are either broadly immune-suppressive (corticosteroids, thiopurines, calcineurin inhibitors) or that target key immune mediators, such as cytokines or integrins.⁴ However, although multiple therapies are currently available, remission rates in UC ostensibly face a therapeutic ceiling with traditional targets.⁵ Thus, there is a need for therapies that target novel aspects of disease pathology in order to enable benefit for additional patients.

Furthermore, it is increasingly appreciated that persistent histologic disease activity is associated with worse disease outcomes for patients with UC.⁶⁻¹⁰ These observations have raised the possibility of a paradigm shift for treatment goals from patient-reported and endoscopic outcomes towards also including evaluation of microscopic disease activity.^{11,12}

The interface between immune function and metabolism is increasingly recognised as fundamental to the inflammatory process.¹³ Alterations in tissue metabolism in the presence of inflammation are associated with increased oxygen consumption and profound tissue hypoxia.¹⁴⁻¹⁶ In chronic inflammation, this circumstance likely occurs as a consequence of increased energy demands by both resident and infiltrating immune cells, in the setting of microvascular damage and dysfunction.^{15,17} Evidence for hypoxia in active gut mucosal inflammation has been demonstrated in mouse models of colitis.^{18,19} Moreover, mucosal hypoxia was recently shown to be correlated with inflammation in patients with UC.²⁰ Multiple lines of evidence support a protective role for hypoxia inducible factor-1 α (HIF-1 α) in response to hypoxia at the epithelial layer of the inflamed gut mucosa.²⁰ HIF-1 α expression correlated with protection from 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis and induced the expression of colonic barrier-protective genes, whereas loss of epithelial HIF-1 α led to severe colonic inflammation in mouse models.¹⁹ Furthermore, pharmacologic stabilisation of HIF-1 α resulted in barrier protective and anti-inflammatory effects in mouse models of colitis, and provided additional evidence for a role for HIF-1 α in tissue remodeling.²¹⁻²³ The results of these studies have in part formed the basis for the novel therapeutic potential for HIF-1 α stabilization to enhance mucosal restitution and wound healing in inflammatory bowel disease.

GB004 (formerly Akebia-4924 or AKB-4924) is an orally administered small molecule that preferentially stabilises HIF-1 α in the gut and is being evaluated as a potential treatment for UC.²⁴⁻²⁶ In animal models of colitis, GB004 treatment stabilised intestinal epithelial cell HIF-1 α , increased expression of HIF-1 α target genes associated with epithelial protection, reduced TNBS-induced intestinal barrier

permeability, and resulted in dose-dependent decreases in mucosal concentrations of inflammatory cytokines (interleukin [IL]-1 β , IL-6 and tumour necrosis factor [TNF]- α).²⁴ Importantly, the protective effects of GB004 were abrogated in intestinal epithelial HIF-1 α deficient mice, demonstrating that epithelial HIF-1 α is required for mucosal protection in this model of colitis.²⁴

In vitro studies using human intestinal differentiated monolayers have also demonstrated stabilisation of HIF-1 α by GB004, with restoration of epithelial monolayer integrity and decreased permeability in response to cytokine stimulation.²⁷ Phase 1a clinical studies of healthy human participants have also provided preliminary evidence for the safety and tolerability of single and multiple ascending doses of GB004.^{28,29} Moreover, the pharmacokinetic profile of GB004 solution was characterised by colonic tissue concentrations that substantially exceeded plasma concentrations (at least 4-fold higher median values) at the time of biopsy in the multiple ascending dose study. This property was accompanied by rapid clearance of GB004 from the systemic circulation, mediated at least in part via glucuronidation and biliary secretion, thus allowing for enterohepatic recirculation, consistent with the finding of high GB004 faecal concentrations. These pharmacokinetic characteristics of GB004 support the potential for a local gut effect with minimal systemic exposure.

Herein we report results from the first-in-patients phase 1b study that examined the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of daily oral treatment with GB004 for 28 days in patients with active UC.

2 | METHODS

2.1 | Study design and treatment

This phase 1b trial (NCT03860896) was a randomised (2:1), double-blind, placebo-controlled, multi-centre study that evaluated a once-daily oral solution of GB004 or placebo administered for 28 days in patients with evidence of active UC. The study employed a 2-cohort design to allow for potential dose adjustment of GB004 in the second cohort. The dose for Cohort 1 was based on the tolerability and safety of GB004 in the phase 1a single- and multiple ascending dose studies in healthy participants and on evidence of target engagement from colonic tissue biopsies in the multiple ascending dose study. In Cohort 1, patients were randomised (2:1) to treatment with GB004 120 mg or placebo once daily. Cohort 2 could be initiated, wherein patients were to be randomised (2:1) to GB004 (at a dose of 120 mg or 60 mg) or placebo once daily, as determined by an internal data review committee.

Eligible patients were randomly assigned to study drug on day 1 by investigators/site personnel via a central interactive response technology (IRT), using computer-generated, permuted block randomisation schedules generated for each cohort by an independent statistician not involved in study conduct. Study sites dispensed identically appearing, blinded, bottled investigational product to

patients, as assigned by the central IRT. Patients, investigators/site personnel, central readers for endoscopy and histology, and the Sponsor were blinded to the randomised treatment. The study was conducted at three sites in the United States, Moldova and Georgia from May to December 2019.

The study protocol was reviewed and approved by the Institutional Review Boards or Independent Ethics Committees of the participating centres in accordance with Good Clinical Practice (GCP) and all applicable regulatory requirements. The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki, and with adherence to the principles of GCP outlined by the International Council for Harmonisation consolidated guidance. All study participants provided informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

2.2 | Participants

Eligible patients included male and female adults (18 to 74 years old) with a body mass index between 18 and 35 kg/m² inclusive, active UC (defined as: total Mayo Clinic score of 3 to 12 with a centrally read Mayo Clinic endoscopy subscore ≥ 1 and presence of blood in the stool [defined as a daily rectal bleeding score ≥ 1 within 1 week prior to randomisation]) diagnosed at least 3 months prior to first dose of study drug and extending at least 15 cm from the anal verge on screening endoscopy, and a Robarts Histopathology Score ≥ 4 with neutrophils in the epithelium (subscore ≥ 1). Patients with mild endoscopic and overall disease severity (Mayo Clinic endoscopy subscore = 1 and total Mayo Clinic score = 3 to 5 respectively) were included to enable evaluation of a broad spectrum of UC severity in this first-in-patient trial assessing GB004. The Mayo Clinic endoscopic subscore and Robarts Histopathology Index score were evaluated by a blinded central reader separately for the rectum and sigmoid colon. For inclusion in the study, the Mayo Clinic endoscopic subscore and Robarts Histopathology Index score were based on the higher scores of either of the two colonic segments. Stable treatment with oral 5-aminosalicylates, corticosteroids (prednisone [≤ 20 mg/day] or equivalent), budesonide Multi-Matrix System [≤ 9 mg/day]), or azathioprine (≤ 3 mg/kg/day) or 6-mercaptopurine (≤ 2 mg/kg/day) for at least 4 weeks prior to randomisation was also required for study inclusion. Patients who received monoclonal antibodies (eg infliximab, golimumab, adalimumab, vedolizumab) used in the treatment of UC, or tofacitinib, oral cyclosporine, tacrolimus, or mycophenolate mofetil within 8 weeks prior to randomisation, or epoetin alfa were ineligible.

2.3 | Study objectives

The primary objective of the study was to evaluate the safety and tolerability of GB004. The secondary objective of the trial was to characterise the pharmacokinetics of GB004 in patients with UC. Exploratory objectives included assessment of GB004 target

engagement and pharmacodynamic response and clinical, endoscopic and histologic activity.

2.4 | Study assessments

2.4.1 | Safety and tolerability

Patients were seen in the clinic weekly (days 1, 7, 14, 21 and 28) throughout the treatment period and 28 days after the last dose of study drug. Safety and tolerability were assessed by evaluating adverse events, and included clinical laboratory assessments, vital signs and 12-lead electrocardiograms. Adverse event severity was assessed by the investigator using Common Terminology Criteria for Adverse Events version 5.0 November 27, 2017.

2.4.2 | Collection of samples

Blood samples were collected for measurement of plasma concentrations of GB004 (pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose on days 1 and 28 and pre-dose on days 7, 14 and 21), as well as for laboratory and biomarker analyses (pre-dose on days 1, 7, 14, 21 and 28). Biopsies were obtained from the rectum and sigmoid at screening and day 28 for measurement of tissue concentrations of GB004, and histologic, immunohistochemical, and gene expression analyses. Stool samples were collected on days 14 and 28 when available.

2.4.3 | Pharmacokinetics

Analysis of plasma, faecal and colonic tissue samples for GB004 concentration determinations was performed using Liquid Chromatography-Mass Spectrometry and Liquid Chromatography-Tandem Mass Spectrometry assays (ICON Laboratory Services, Whitesboro, NY USA). The GB004 analytical range was 1.00-1000 ng/mL for plasma, 10.0-10 000 ng/g for faecal and 1.00-1000 ng/g for tissue samples. Sample results below 1.00 ng/mL, 10.0 ng/g or 1.00 ng/g were reported as below the limit of quantitation for plasma, faecal or tissue samples respectively. During analysis of the study samples, the assays showed acceptable performance as demonstrated by plasma quality control sample mean accuracies (percent relative error) $\leq \pm 6.50\%$ and precision (coefficient of variation) $\leq 10.1\%$, faecal quality control sample mean accuracies $\leq \pm 5.33\%$ and precision $\leq 5.84\%$, and tissue quality control sample mean accuracies $\leq \pm 4.27\%$ and precision $\leq 5.74\%$ across all concentration levels.

2.4.4 | Pharmacodynamics

Detailed methods for immunohistochemical and enzyme-linked immunosorbent assays used for pharmacodynamic analysis of

tissue and faecal samples are included in the Supplementary Material.

2.4.5 | Efficacy

Efficacy assessments included the total Mayo Clinic score, comprised of stool frequency, rectal bleeding, physician's global assessment, and endoscopic subscores and the Robarts Histopathology Index score. Scores on the latter instrument range from 0-33 with higher scores denoting greater disease severity.

Stool frequency and rectal bleeding subscores were captured from daily paper dairies and were calculated based upon the most recent 3 days with data in the 7 days prior to the study visit, excluding the days of and after endoscopy, and the day(s) of bowel preparation at the screening and day 28 visits. The physician's global assessment was performed at each visit. Endoscopic and histologic disease activity were evaluated by blinded central review at the screening and day 28 visits.

Efficacy endpoints evaluated at day 28 included the proportions of patients with: clinical response, defined as a reduction from baseline in total Mayo Clinic score (using the sigmoid endoscopic subscore among patients with a baseline sigmoid endoscopic subscore ≥ 1) of ≥ 3 points and ≥ 30 percent, with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point (among patients with a baseline rectal bleeding subscore ≥ 1); clinical remission, defined as a total Mayo Clinic score ≤ 2 (using the sigmoid endoscopic subscore among patients with a baseline sigmoid endoscopic subscore ≥ 1), with no individual subscore > 1 ; rectal bleeding resolution, defined as a rectal bleeding subscore of 0 (among patients with a baseline rectal bleeding subscore ≥ 1); improvement in endoscopic appearance, defined as a sigmoid or rectum endoscopic subscore ≤ 1 (if corresponding baseline endoscopic subscore > 1) or 0 (if corresponding baseline endoscopic subscore = 1); histologic remission, defined as a sigmoid or rectum Robarts Histopathology Index score ≤ 3 with lamina propria neutrophils and neutrophils in epithelium subscores of 0 (among patients with corresponding baseline lamina propria and neutrophils in epithelium subscores > 0); and mucosal healing, defined as achieving both improvement in endoscopic appearance and histologic remission in the same colonic segment.

Composite efficacy endpoints at day 28 were evaluated on a post hoc basis. The first set of composite endpoints included the proportions of patients concurrently achieving: rectal bleeding resolution and histologic remission; rectal bleeding resolution, clinical response, and histologic remission; and rectal bleeding resolution, clinical response, histologic remission and molecular improvement. Molecular improvement was defined based on the PROTECT UC gene signature (see Supplementary Material for additional information) containing 712 genes, whose development and validation was based on association with the presence of UC, clinical and endoscopic severity, and ability to predict clinical remission.³⁰ The second set of composite endpoints was defined

similarly to the first, but with histologic remission replaced by mucosal healing.

2.5 | Statistical analysis

The sample size was not based upon statistical considerations. If Cohort 2 was initiated, statistical analyses were to be performed by pooling the placebo groups across both cohorts, and if the GB004 dose selected for Cohort 2 was 120 mg, statistical analyses were to be performed by pooling the GB004 treatment groups across both cohorts. The safety population included all patients who received at least one dose of the study drug. The pharmacokinetic population included all patients who received at least one dose of GB004 with evaluable pharmacokinetic data. Plasma pharmacokinetic parameters for GB004 were derived from plasma concentrations for days 1 and 28 separately using actual time of sample collections by standard noncompartmental methods, using Phoenix WinNonlin[®] release 6.3 (Certara USA, Inc, Princeton, NJ, USA). Efficacy and pharmacodynamic analyses were performed using the intent-to-treat population, defined as all randomised patients who received at least one dose of study drug. Results were summarised descriptively, and no formal statistical hypothesis testing was performed. Efficacy analyses were based on evaluable patients, using non-responder imputation (missing value considered as not meeting the endpoint), with 95% confidence intervals (CI) for treatment effect estimates based on the exact method of Chan and Zhang.³¹ Pharmacodynamic analyses summarised treatment effect estimates for faecal calprotectin and secretory immunoglobulin A using differences in median percent change from baseline based on quantile regression employing a simplex optimisation algorithm,³² with 95% CIs based on the inverted rank-score method, and differences in mean change from baseline for proportion of HIF-1 α and MPO-positive cells, with 95% CIs based on t-distribution. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina, USA) and R Statistical Software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Patients

Following the review of Cohort 1 data, the internal data review committee recommended the initiation of Cohort 2 at the 120 mg dose of GB004. Overall, a total of 46 patients were screened for study eligibility, of which, 34 (73.9%) were randomised to treatment with GB004 120 mg ($n = 23$) or placebo ($n = 11$) (Figure 1), with 17 patients randomised in each cohort. Of the 34 patients comprising the safety population, 33 (97.1%) completed the study. One patient (4.3%) treated with GB004 discontinued treatment and withdrew from the study due to lack of efficacy for worsening UC.

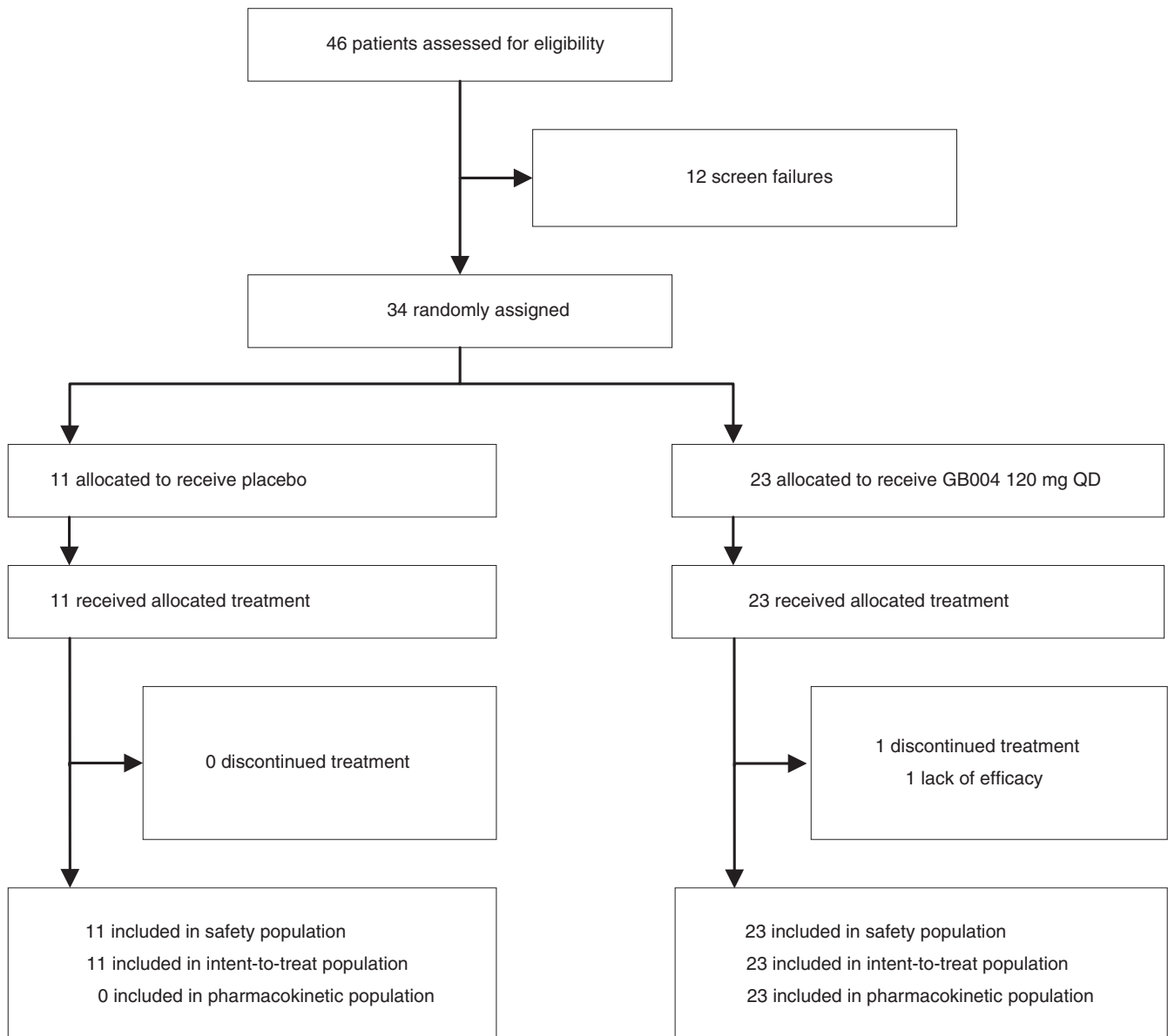


FIGURE 1 Patient disposition

Baseline demographics and disease characteristics were generally similar between the treatment groups (Table 1). Mean (SD) age was 45.4 (12.71) years, and most patients were male (67.6%) and white (91.2%). Mean (SD) time since UC diagnosis was 5.59 (6.109) years. The mean (SD) baseline total Mayo Clinic score was 7.5 (2.00) based on the appearance of the sigmoid colon. Mean (SD) baseline Roberts Histopathology Index scores were 14.1 (18.63) and 17.4 (8.94) based on sigmoid and rectum biopsy, respectively, representing moderate histologic activity.

All patients had received prior treatment with 5-aminosalicylates and 58.8% (20/34) had previously received corticosteroids (prednisone, prednisolone, methylprednisolone or budesonide MMX), whereas prior treatment with immunosuppressants or biologics was less common (29.4% [10/34] and 2.9% [1/34] overall respectively). One GB004-treated patient (4.3%) received prior anti-tumour

necrosis factor alpha treatment. A higher percentage of patients in the GB004 group (26.1% [6/23]) were receiving ongoing corticosteroids at baseline compared with patients in the placebo group (0 patients), and 1 (4.3%) patient in the GB004 group was receiving ongoing treatment with an immunosuppressant (azathioprine) at baseline compared with no patients in the placebo group.

3.2 | Safety and tolerability

Daily oral doses of GB004 120 mg for 28 days were generally well-tolerated (Table 2). The overall incidence of adverse events was 27.3% (3/11) among patients treated with placebo and 39.1% (9/23) among patients treated with GB004. The majority of GB004-treated patients with adverse events had Grade 1 (mild) events. The

TABLE 1 Baseline demographics and disease characteristics

	Placebo (n = 11)	GB004 120 mg (n = 23)
Age (years), mean (SD)	45.5 (15.42)	45.4 (11.58)
Male sex, n (%)	8 (72.7)	15 (65.2)
Body mass index (kg/m ²), mean (SD)	23.51 (3.237)	25.86 (3.868)
Race, White n (%)	9 (81.8)	22 (95.7)
Black or African American	1 (9.1)	1 (4.3)
Asian	1 (9.1)	0
Years since diagnosis, mean (SD)	4.55 (6.089)	6.09 (6.190)
Extent of disease, n (%)		
Extensive	8 (72.7)	11 (47.8)
Prior UC treatments, n (%)		
5-aminosalicylates	11 (100.0)	23 (100.0)
Corticosteroids (prednisone, prednisolone, methylprednisolone, budesonide MMX)	6 (54.5)	14 (60.9)
Immunosuppressants	2 (18.2)	8 (34.8)
Prior anti-tumour necrosis factor agents	0	1 (4.3)
Ongoing UC treatments, n (%)		
Corticosteroids	0	6 (26.1)
Immunosuppressants	0	1 (4.3)
Faecal calprotectin, µg/g, median (range)	1955.0 (52, 11 492)	1336.0 (79, 13 596)
Mayo Clinic score (using sigmoid endoscopic subscore), mean (SD)	7.6 (1.91)	7.4 (2.08)
Mild disease (3-5)	1 (9.1)	4 (17.4)
Moderate disease (6-10)	10 (90.9)	18 (78.3)
Severe disease (11-12)	0	1 (4.3)
Stool frequency subscore, mean (SD)	1.8 (0.87)	2.0 (0.80)
Rectal bleeding subscore, mean (SD)	1.3 (0.47)	1.0 (0.43)
Sigmoid endoscopic subscore, mean (SD)	2.4 (0.92)	2.1 (0.97)
Rectum endoscopic subscore, n (%)	2.5 (0.82)	2.4 (0.78)
Robarts Histopathology Index score (sigmoid), mean (SD)	14.5 (8.97)	14.0 (8.66)
Robarts Histopathology Index score (rectum), mean (SD)	19.5 (10.20)	16.3 (8.32)

incidence of treatment-related adverse events was higher among patients treated with GB004 compared with patients treated with placebo (30.4% [7/23] vs 9.1% [1/11]). There were no treatment-related serious adverse events or deaths in the study. One patient (4.3%) treated with GB004 experienced a serious adverse event of worsening UC that led to treatment discontinuation and study withdrawal. This event was assessed as unrelated to GB004.

The most commonly reported adverse events in patients treated with GB004 were nausea (5/23 patients [21.7%] vs 0 patients treated with placebo) and dysgeusia (3/23 patients [13.0%]

TABLE 2 Summary of safety and tolerability

	Placebo (n = 11) n (%)	GB004 120 mg (n = 23) n (%)
Incidence of adverse events	3 (27.3)	9 (39.1)
Incidence of adverse events of CTCAE Grade 2 or higher	2 (18.2)	4 (17.4)
Incidence of serious adverse events	0	1 (4.3)
Incidence of treatment-related adverse events	1 (9.1)	7 (30.4)
Incidence of treatment-related serious adverse events	0	0
Incidence of adverse events leading to study drug discontinuation/withdrawal	0	1 (4.3)
Incidence of adverse events by preferred term ≥5% in either treatment group		
Nausea	0	5 (21.7)
Dysgeusia	0	3 (13.0)
Dizziness	1 (9.1)	1 (4.3)
Iron deficiency anaemia	1 (9.1)	1 (4.3)
Fatigue	1 (9.1)	0

Abbreviation: CTCAE, common terminology criteria for adverse events.

vs. 0 patients treated with placebo) (Table 2). All events of nausea and dysgeusia that were considered related to GB004 were reported as Grade 1 (mild) in severity; one event of nausea was considered not related and was reported as Grade 2 (moderate) in severity. All treatment-emergent adverse events occurring at an incidence ≥5% (Table 2) resolved. There were no vital sign or electrocardiogram changes related to study drug, and there was no clear or discernable difference between the treatment groups regarding laboratory measurements, including chemistry, haematology, urinalysis, iron, erythropoietin and vascular endothelial growth factor parameters.

3.3 | Pharmacokinetics and biomarkers

Plasma concentrations of GB004 were similar on days 1 and 28 following single and multiple oral dose administration of GB004 120 mg, respectively, and minimal accumulation of GB004 was observed after 28 days of once-daily dosing. Faecal concentrations of GB004 were comparable on days 14 and 28. Geometric mean sigmoid and rectal colonic tissue concentrations of GB004 on day 28 were similar, with high variability, and greater than those in plasma (approximately 6 and 65 times higher than peak and average plasma concentrations).

Exploratory analyses of target engagement and pharmacodynamic response showed that treatment with GB004 was associated with changes in biomarker expression from baseline to day 28

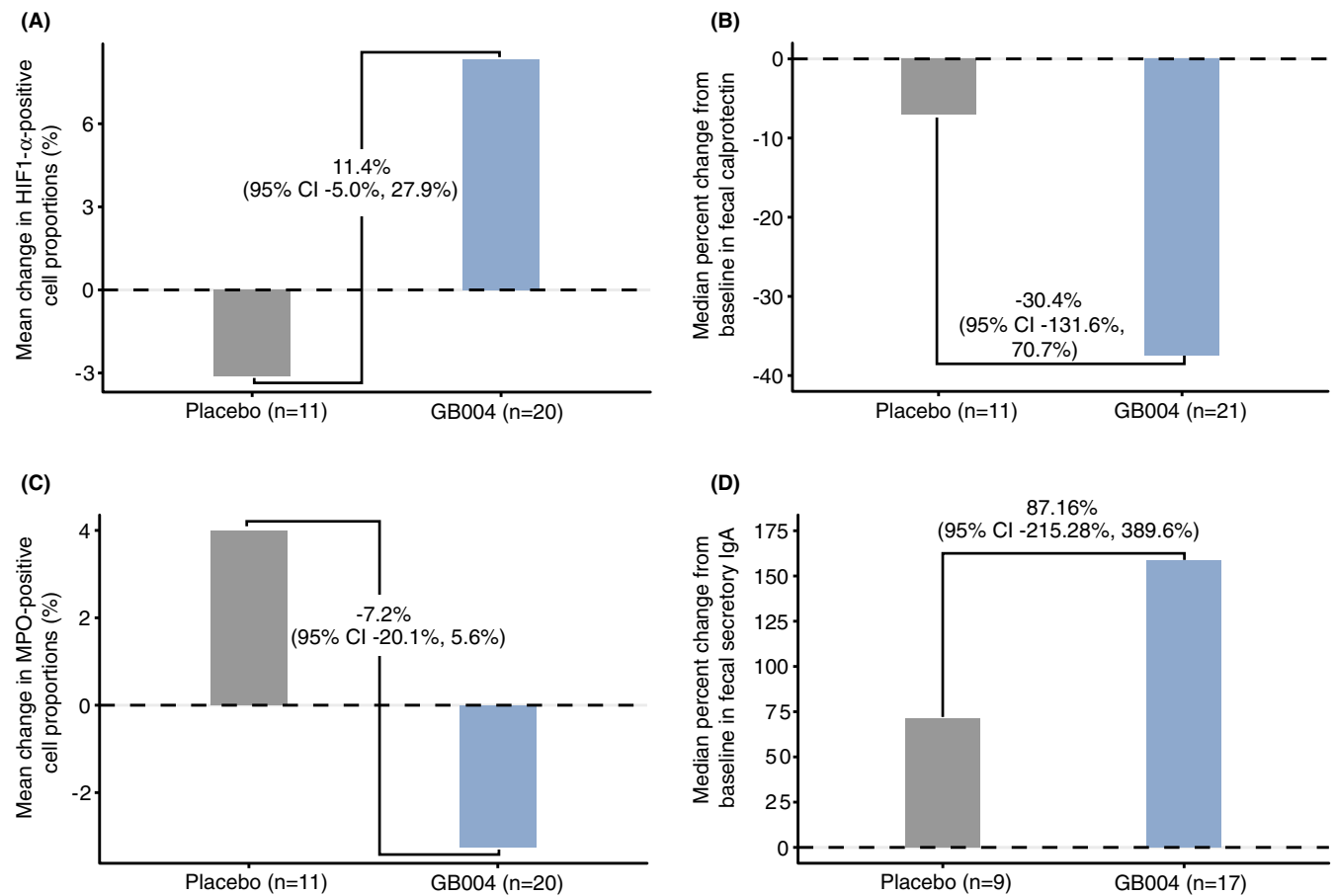


FIGURE 2 Changes from baseline to day 28 in pharmacodynamic measures of GB004 target engagement and biomarkers. (A) proportion of HIF-1 α -positive cells; (B) faecal calprotectin; (C) proportion of MPO-positive cells; (D) faecal secretory immunoglobulin A. Analyses were based on observed data. Treatment effect estimates (95% CIs) are shown as differences between GB004 and placebo. Abbreviations: HIF, hypoxia inducible factor; MPO, myeloperoxidase

(Figure 2). An increase in mean HIF-1 α positive cell proportions in sigmoid colon biopsies was observed in the GB004 group relative to the placebo group (difference: 11.4%; 95% CI: -5.0%, 27.9%), supportive of local target engagement. Faecal calprotectin, a surrogate marker of mucosal inflammation, decreased in the GB004 group relative to the placebo group (difference in median percent change from baseline: -30.4%; 95% CI: -131.6%, 70.7%). A decrease in mean myeloperoxidase-positive cell proportions in sigmoid colon biopsies was also observed (difference: -7.2%; 95% CI: -20.1%, 5.6%), consistent with a reduction in mucosal inflammation in patients assigned to treatment with GB004. Additionally, an increase in faecal secretory immunoglobulin A concentration was observed (difference in median percent change from baseline: 87.16%; 95% CI: -215.28%, 389.60%). This biomarker is associated with barrier homeostasis and local immune defence.³³⁻³⁵

3.4 | Exploratory efficacy endpoints

This phase 1b study was not powered to detect differences between treatment groups for efficacy endpoints; however, most

exploratory efficacy analyses numerically favoured treatment with GB004 120 mg compared with placebo (Figure 3A,B) when taking into account estimated treatment effects and their associated variability.

Clinical disease activity endpoints favouring GB004 treatment at day 28 included clinical response and rectal bleeding resolution. Clinical response was observed in 30.0% of patients (6/20) in the GB004 group and 18.2% (2/11) in the placebo group (difference, 11.8%; 95% CI: -24.9%, 41.3%). Rectal bleeding resolution was achieved in 57.1% (12/21) of patients in the GB004 group and 36.4% (4/11) in the placebo group (difference, 20.8%; 95% CI: -18.4%, 53.8%). Clinical remission was achieved in 4.5% (1/22) of patients in the GB004 group and no patients (0/11) in the placebo group.

Endoscopic and histologic endpoints assessed at day 28 included improvement in endoscopic appearance, histologic remission, and mucosal healing. A similar proportion of patients in each treatment group had an improvement in endoscopic appearance (GB004, 17.4% [4/23] vs placebo, 18.2% [2/11]), however, histologic remission was achieved in a higher proportion of patients in the GB004 group: 43.5% (10/23) vs 18.2% (2/11) in the placebo

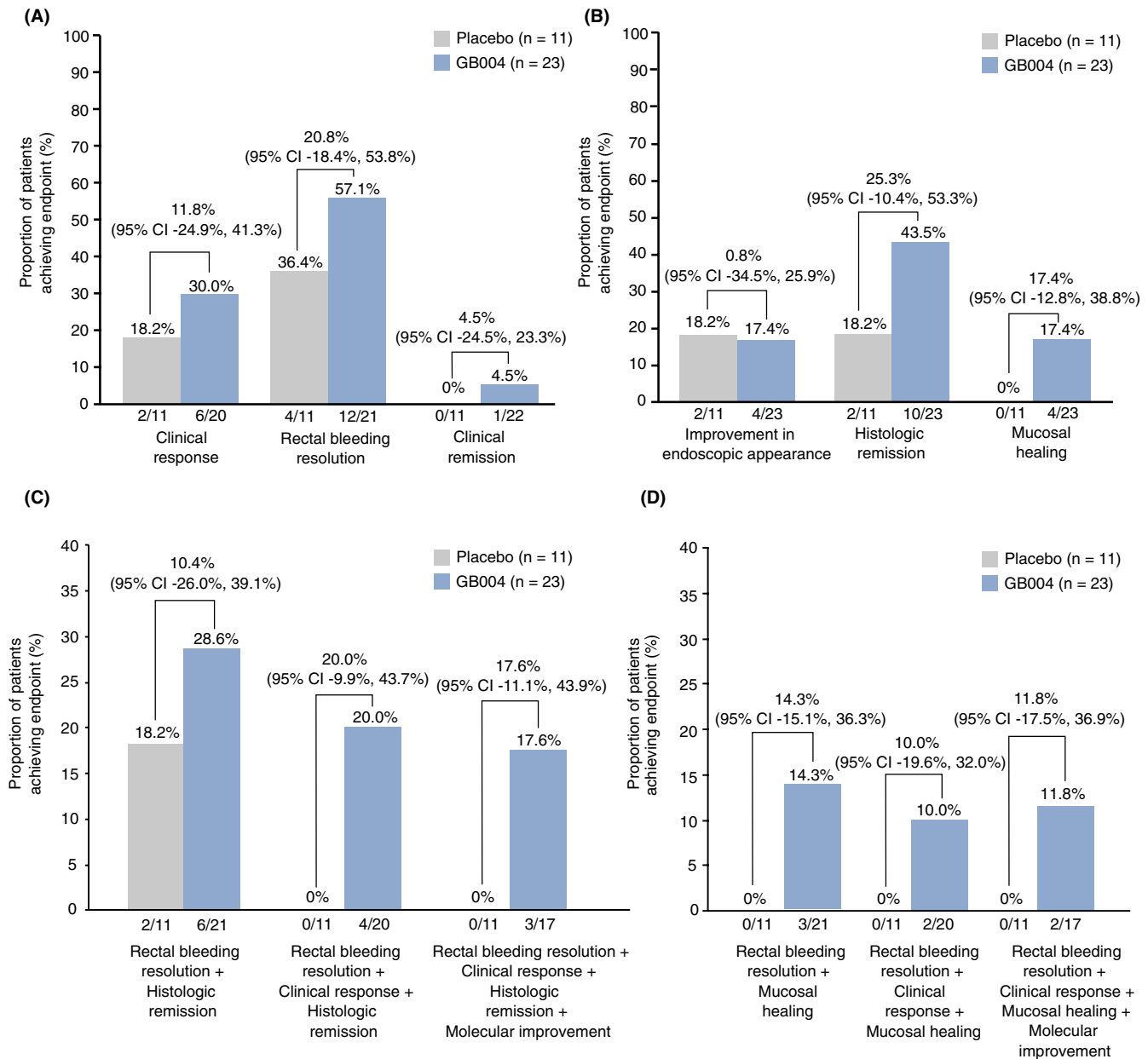


FIGURE 3 Exploratory efficacy endpoints at day 28. (A) clinical response, rectal bleeding resolution, and clinical remission; (B) improvement in endoscopic appearance; histologic remission; and mucosal healing; (C) composite endpoints requiring concurrent achievement of: rectal bleeding resolution and histologic remission; rectal bleeding resolution, clinical response, and histologic remission; and rectal bleeding resolution, clinical response, histologic remission, and molecular improvement; (D) composite endpoints requiring concurrent achievement of: rectal bleeding resolution and mucosal healing; rectal bleeding resolution, clinical response, and mucosal healing; and rectal bleeding resolution, clinical response, mucosal healing, and molecular improvement. Proportions are the number of patients meeting the endpoint out of the number evaluable. Evaluable patients with missing values for an endpoint were considered as not meeting the endpoint (0 patients in the placebo group, and 2 patients in the GB004 group for all endpoints in (A) and (B), with the exceptions of clinical response and clinical remission [3 patients each]). One patient in the GB004 group meeting the composite endpoint of rectal bleeding resolution and clinical response and histologic remission or mucosal healing had missing gene expression data. Treatment effect estimates (95% CIs) are shown as differences between GB004 and placebo

group (difference, 25.3%; 95% CI: -10.4%, 53.3%). The more stringent endpoint of mucosal healing, requiring both an improvement in endoscopic appearance and histologic remission, was achieved in 4/23 (17.4%) patients in the GB004 group, whereas no patient in the placebo group (0/11) achieved mucosal healing (difference, 17.4%; 95% CI: -12.8%, 38.8%).

Analyses of composite endpoints assessed at day 28 on a post hoc basis, requiring concurrent achievement of multiple clinical disease activity, endoscopic, histologic and molecular endpoints, also numerically favoured GB004 and resulted in minimising placebo response, with observed differences for GB004 vs placebo ranging from 10.0% to 20.0% (Figure 3C,D).

4 | DISCUSSION

Defective barrier function is believed to be central to the pathogenesis of inflammatory bowel disease. Thus, evaluation of GB004, which directly affects the restoration of the intestinal barrier, as a treatment for active UC offers a novel and promising approach. Consistent with observations from studies in healthy participants, the results of this phase 1b, first-in-patient study provide evidence for the safety and tolerability and low systemic exposure associated with GB004 treatment. GB004 was generally well tolerated when orally administered at 120 mg once daily for 28 days to patients with UC, with 95.7% (22/23) of GB004-treated patients completing treatment. While nausea and dysgeusia occurred more frequently in patients treated with GB004, these events were all classified as mild, with one exception, and none of these events led to GB004 discontinuation or study withdrawal. There were no discernable differences between treatment groups in any of the laboratory parameters assessed in the study, including erythropoietin and vascular endothelial growth factor. The minimal adverse effects observed with short-term treatment with GB004 in this study may, in part, be related to the modest systemic accumulation after 28 days of once-daily dosing. Potential lack of systemic immunosuppression may have also contributed to the overall safety profile for GB004.

The substantially higher colonic concentrations of GB004 relative to plasma concentrations observed in this study support a local gut effect of GB004, likely driven by enterohepatic recirculation, the latter of which is evidenced by high faecal concentrations of GB004. The potential safety benefit of this local effect is also apparent in an absence of increased systemic levels of erythropoietin or vascular endothelial growth factor relative to placebo. Importantly, this observation distinguishes GB004 from systemic prolyl hydroxylase domain enzyme inhibitors in development or approved for the treatment of anaemia in chronic kidney disease, as these agents have been shown to increase systemic concentrations of erythropoietin and stimulate erythropoiesis.³⁶⁻³⁹

Exploratory biomarker and efficacy results from this phase 1b study of GB004 support the biologic relevance and therapeutic potential of this novel approach for the treatment of UC. Target engagement was demonstrated by GB004-dependent increases in HIF-1 α positive cell proportions in the sigmoid colon. Increased levels of faecal secretory immunoglobulin A in response to GB004 treatment also suggest improvements in local gut epithelial immune defence. The observed decreases in disease activity biomarkers myeloperoxidase and faecal calprotectin following GB004 treatment are consistent with results observed for efficacy endpoints evaluated. Numerically higher proportions of patients treated with GB004 experienced improvements in measures of disease activity compared with placebo, including the stringent endpoint of mucosal healing.

This phase 1b study included a novel design that required baseline histologic evidence for the presence of neutrophils in the epithelium, a hallmark for histologically active UC.⁴⁰ The significance of histologic remission as a therapeutic goal in UC has been

underscored in numerous recent studies given that persistence of microscopic inflammation despite a normal endoscopic appearance is associated with clinical relapse, hospitalisation, corticosteroid use, colectomy, and development of colorectal cancer.^{6,8,9,41} Assessment of histologic disease activity in patients with UC is therefore becoming an important aspect of disease monitoring in clinical trials and may eventually also play a role in therapeutic decision-making.^{11,12}

Notably, evaluation of composite endpoints on a post hoc basis demonstrated preliminary evidence of GB004's effect across a breadth and depth of multiple aspects of UC disease burden, as defined by concurrent achievement of symptomatic improvement, histologic remission/mucosal healing and molecular improvement. The use of these composite endpoints also minimised placebo response, and, as such, may enhance signal detection in future early phase UC studies. Furthermore, such composite endpoints are congruent with evolving therapeutic goals in UC.⁴² To the best of our knowledge, this is the first UC clinical trial to evaluate composite endpoints including a molecular component assessing restoration of specific pathways involved in the aetiopathogenesis of UC.

This study had several limitations. It was a phase 1b study aimed at characterising safety and pharmacokinetics, with biomarker and efficacy evaluations being exploratory, and it had a relatively short duration of 4 weeks of treatment and relatively small sample size compared to typical phase 2 and 3 UC studies. Despite these limitations, the results of this study suggest the potential for GB004 as a treatment for UC.

In conclusion, this study provides encouraging early phase results that support additional research into the full therapeutic potential of GB004 for patients with UC. To this end, the efficacy and safety of GB004 as an oral tablet formulation at higher doses and for a longer treatment duration are currently being investigated for the treatment of mild-to-moderate UC despite treatment with 5-aminosalicylates in the ongoing phase 2 SHIFT-UC study (NCT04556383).

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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