CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, randomized, double-blind, placebo-controlled, multi-center study to evaluate GB004 in adult subjects with mild-to-moderate active ulcerative colitis
Short Title:	GB004 in adult subjects with active ulcerative colitis
Protocol Number:	GB004-2101
Compound Number:	GB004
Study Phase:	Phase 2
Sponsor Name:	GB004, Inc.
Legal Registered Address:	3013 Science Park Road San Diego, CA 92121, USA
Regulatory Agency Identifier Number(s):	**IND Number:** 133519 **EudraCT:** 2020-002306-12
Version:	3.0, Amendment 2.0
Approval Date:	15 December 2021

Sponsor's Authorized Representative Signature Page

GB004-2101

A Phase 2, randomized, double-blind, placebo-controlled, multi-center study to evaluate GB004 in adult subjects with mild-to-moderate active ulcerative colitis

[redacted]

Medical Monitor name and contact information will be provided separately.

INVESTIGATOR AGREEMENT

GB004-2101: A Phase 2, randomized, double-blind, placebo-controlled, multi-center study to evaluate GB004 in adult subjects with mild-to-moderate active ulcerative colitis.

I, the undersigned, have read this protocol and agree to conduct this protocol in accordance with ethical principles as outlined in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements and any additional conditions mandated by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I acknowledge that I am responsible for the overall study conduct and I agree to personally conduct or supervise the described clinical study.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GB004, Inc.

_____

Signature

_____ _____

Name of Investigator Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2.0 (v3.0)	15 December 2021
Amendment 1.0 (v2.0)	21 October 2020
Original Protocol (v1.0)	27 July 2020

Amendment 2.0 (v3.0, 15 December 2021)

Overall Rationale for the Amendment:

The purpose of this amendment is primarily to make updates to Section 6.8 (Concomitant Medications) and Appendix 6 (Prohibited Medications).

Table 1: Summary of Changes

Section # and Name	Description of Change	Brief Rationale
6.8 Concomitant Therapy	Guidance has been added regarding the use of sensitive clinical substrates of OCT2 and CYP2C8 with GB004.	Results from in vitro studies indicate that a glucuronide metabolite of GB004, GBD242, may be an inhibitor of OCT2 and CYP2C8.
Appendix 6	Added dofetilide and sensitive substrates of CYP2C8 to Prohibited Medications.	Concomitant use of dofetilide, which is contraindicated when used with OCT2 inhibitors, is prohibited in this study. Concomitant use of sensitive substrates of CYP2C8 (eg, repaglinide, rosiglitazone, pioglitazone, and loperamide) is prohibited in this study.
1.3.2 Open-Label Extension – Schedule of Activities	Added Physician's Global Assessment (PGA) at the OLE Follow-up visit.	This assessment should occur at the OLE Follow-up visit.
1.2 Study Schema	Edited text in study schema for consistency with protocol text.	For overall clarity and alignment with protocol text.
4.1.2 OLE (24 Weeks)	Added text "(if last dose of PCP IP has not been taken earlier in the day)" to the second sentence of the second paragraph.	The change was made for clarity.
5.2 Exclusion Criterion #22	Estimated glomerular filtration rate (eGFR) was corrected to read < 60 mL/min/1.73 m^2.	Change was made to correct an earlier oversight.

9.4.1.1 Efficacy Analysis, Secondary Endpoints	The second sentence was updated to read: Histologic remission at PCP Week 12 and mucosal healing at PCP Week 12 will be evaluated among subjects with Baseline lamina propria neutrophils and neutrophils in epithelium RHI subscores > 0.	Change was made to correct an earlier oversight.
9.5 Interim Analysis 1.1 Synopsis 4.1.1 Placebo-Controlled Period (36 weeks)	Text related to the optional, unblinded interim analysis was removed.	The interim analysis is no longer planned.
4.1.1 Placebo-Controlled Period (36 weeks)	Removed the following sentence: "Subjects who permanently discontinue IP or withdraw from study during the PCP will not be eligible to enter the OLE."	The sentence was removed for clarity and because Section 4.1.2 clearly describes who is eligible for the OLE.
4.1.1 Placebo-Controlled Period (36 weeks)	Added text "without enrolling in the OLE" to the paragraphs discussing subjects who permanently discontinue IP and subjects who withdraw from the PCP.	These changes were made for clarity.
7.1 Discontinuation	Added text "if the subject is not enrolling in the OLE" to the paragraph discussing Discontinuation of IP during the PCP.	This change was made for clarity.
Other minor corrections to grammatical or typographical errors were made that did not affect content.		

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2, randomized, double-blind, placebo-controlled, multi-center study to evaluate GB004 in adult subjects with mild-to-moderate active ulcerative colitis

Short Title: GB004 in adult subjects with active ulcerative colitis

Rationale

GB004 (formerly AKB-4924) is a novel small molecule in development for the treatment of inflammatory bowel disease (IBD). The novel approach of GB004 is based on evidence that hypoxia inducible factor 1 alpha (HIF-1α), a member of the hypoxia inducible factor (HIF) transcription factor family, has a crucial role in the maintenance of epithelial barrier integrity and in the modulation of the innate inflammatory response in mouse models of IBD.

Small molecule prolyl hydroxylase inhibitors (PHDi's) stabilize HIF-1α protein and have shown efficacy in multiple mouse models of IBD that include trinitrobenzene sulfonic acid (TNBS) and dextran sulfate sodium (DSS)-induced colitis models and the tumor necrosis factor alpha (TNFα)-driven terminal ileitis model (Ablin, 1999; Minaiyan, 2012). Prolyl hydroxylases (PHDs) are key regulators of the HIF pathway (Eltzschig, 2014). These findings support PHD inhibition as a target for treating ulcerative colitis (UC).

GB004, a HIF-1α stabilizer, is being developed as an oral therapeutic, gut-targeted treatment for UC with higher intestinal than systemic exposure. The relatively low oral bioavailability (< 20%) and preferential distribution to the gastrointestinal (GI) tissues observed in nonclinical studies, combined with its mechanism of action in gut lumen and positive effects on gut healing and inflammation in animal models of colitis, provide rationale for further development in human subjects.

GB004 has been shown in studies of both healthy volunteers (AKB-4924-CI-1001, AKB-4924-CI-1002, and GB004-1902) and patients with UC (GB004-1101) to be a gut-targeted treatment with higher intestinal than systemic exposure. In addition, the GB004-1101 study, although limited by only 4 weeks of dosing, showed trends in improvement in clinical and histologic outcomes in UC patients. GB004, Inc. has developed tablet formulations with 2 release profiles, tablets and delayed-release (DR) tablets, which have distinct systemic profiles with both delivering GB004 to the colonic tissue.

This 2-part study, comprising of a 36-week placebo-controlled period and a 24-week open-label extension period, will assess the efficacy and safety of GB004 when added to background UC therapy of 5-aminosalicylate (5-ASA) with or without systemic steroids.

Objectives and Endpoints

Placebo-Controlled Period (PCP) (Primary, Secondary and Safety Objectives and Endpoints)

Objectives	Endpoints
Primary	
• To evaluate the effect of GB004 compared to placebo on clinical remission at PCP Week 12	• Proportion of subjects with clinical remission at PCP Week 12, defined as a Modified Mayo score ≤ 2, with a Rectal bleeding subscore of 0, Stool frequency subscore of 0 or 1 (with a ≥ 1 point decrease from baseline), and Endoscopic subscore of 0 or 1
Secondary	
• To evaluate the effect of GB004 on clinical response, histologic remission, endoscopic improvement, mucosal healing at PCP Week 12	• Proportion of subjects with clinical response at PCP Week 12, defined as reduction in the Modified Mayo score of ≥ 2 points and ≥ 35 percent reduction from baseline, including a decrease in Rectal bleeding subscore of ≥1 or absolute Rectal bleeding subscore of ≤ 1 • Proportion of subjects with histologic remission at PCP Week 12, defined as Robarts Histopathology Index (RHI) ≤ 3 with lamina propria neutrophils subscore = 0 and neutrophils in epithelium subscore = 0 • Proportion of subjects with endoscopic improvement at PCP Week 12, defined as endoscopic subscore of 0 or 1 • Proportion of subjects with mucosal healing at PCP Week 12, defined as endoscopic improvement and histologic remission
• To evaluate the effect of GB004 on clinical remission, clinical response, histologic remission, endoscopic improvement, and mucosal healing at PCP Week 36	• Proportion of subjects with clinical remission at PCP Week 36 • Proportion of subjects with clinical response at PCP Week 36 • Proportion of subjects with histologic remission at PCP Week 36 • Proportion of subjects with endoscopic improvement at PCP Week 36 • Proportion of subjects with mucosal healing at PCP Week 36
Safety	
• To evaluate the safety and tolerability of GB004	• Incidence of treatment-emergent adverse events (TEAEs)

Open-Label Extension (OLE) (Primary)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GB004	• Incidence of TEAEs

Overall Design

This is a 2-part study in adult subjects with mild-to-moderate active UC who have disease activity despite treatment with 5-ASA with or without systemic steroids:

- The Placebo-Controlled period (PCP) is a randomized, placebo-controlled, multi-center, 36-week study evaluating the efficacy, safety, tolerability and pharmacokinetics (PK) of 2 dose regimens of GB004; the initial 12 weeks of treatment will be double-blind.
- The OLE is an open-label, multi-center, 24-week study evaluating the safety and tolerability of GB004 twice per day (BID) dose regimen

Subjects who complete the Week 36 visit on IP and subjects who meet the predefined UC Disease Activity criteria at or after PCP Week 12 visit and prior to PCP Week 36 visit on IP can enter the OLE (for details refer to Section 5.3).

All subjects participating in the study will be required to maintain a stable dose of 5-ASA throughout the study. Subjects on systemic corticosteroids must remain on a stable dose during the initial 12 weeks of the PCP (for details refer to Section 6.5.2). After the PCP Week 12 visit, a standardized taper from systemic corticosteroids may be attempted at any time.

All subjects will attend a Follow-up visit at the clinic 4 weeks after last dose of IP.

A data review committee (DRC) will periodically convene to review unblinded overall safety and emerging efficacy results (Section 9.5.1).

A schematic of the study design is presented in Section 1.2.

Placebo-Controlled Period (36 weeks)

After signing an informed consent form (ICF), subjects will be screened for study eligibility over a Screening period of up to 5 weeks. During the Screening period, subjects will capture stool frequency and rectal bleeding symptoms in a provided electronic diary (eDiary) on a daily basis. Flexible sigmoidoscopy or colonoscopy will be performed at screening. Subjects not meeting the eligibility criteria will be deemed screen failures and will not continue participation in the study.

On Day 1/Week 0, eligible subjects will be randomized 1:1:1 to receive the following treatments for 36 weeks:

- GB004 480 mg BID
- GB004 480 mg once daily (QD)
- Placebo

Randomization will be stratified by systemic corticosteroid use at baseline (yes/no).

All subjects will dose investigational product (IP) BID to maintain the blind (for details refer to Section 6.1).

The first dose of IP will be administered in the clinic on Day 1/Week 0 with food. All subsequent doses will be taken at home with food with the exception of the morning doses at the Week 2, 4, 8, 12, and 36 visits where IP will be administered in the clinic, with food, after predose blood collection as specified in the Schedule of Activities (SoA) in Section 1.3.1 – PCP.

After initiation of IP on Day 1/Week 0, subjects will return to the clinic and will be evaluated as specified in the SoA, see Section 1.3.1. A flexible sigmoidoscopy with biopsies will be performed at the PCP Week 12 and Week 36 visits (and at an Unscheduled UC Disease Activity Criteria Assessment visit(s) and the Early Withdrawal from Study visit, if applicable).

OLE (24 weeks)

Subjects may participate in the 24-week OLE if in the opinion of the Investigator they have been compliant with study procedures and:

- Completed the Week 36 visit on IP; or
- Met the predefined UC Disease Activity criteria any time after PCP Week 12 visit and prior to PCP Week 36 visit on IP (refer to Section 5.3)

Beginning at the OLE Enrollment visit, all subjects will receive GB004 480 mg BID for 24 weeks. All doses will be taken at home with food with the exception of the morning dose at the OLE Enrollment visit, OLE Week 2, 12 and End of OLE visit/Early termination (ET) visit where IP will be administered in the clinic, with food, after predose blood collection as specified in the SoA (Section 1.3.2 – OLE). Subsequently, subjects will return to the clinic and be evaluated as specified in the SoA (Section 1.3.2 - OLE).

Number of Participants and Intervention Groups

The study will randomize approximately 195 subjects, with approximately 65 subjects per treatment group in the PCP.

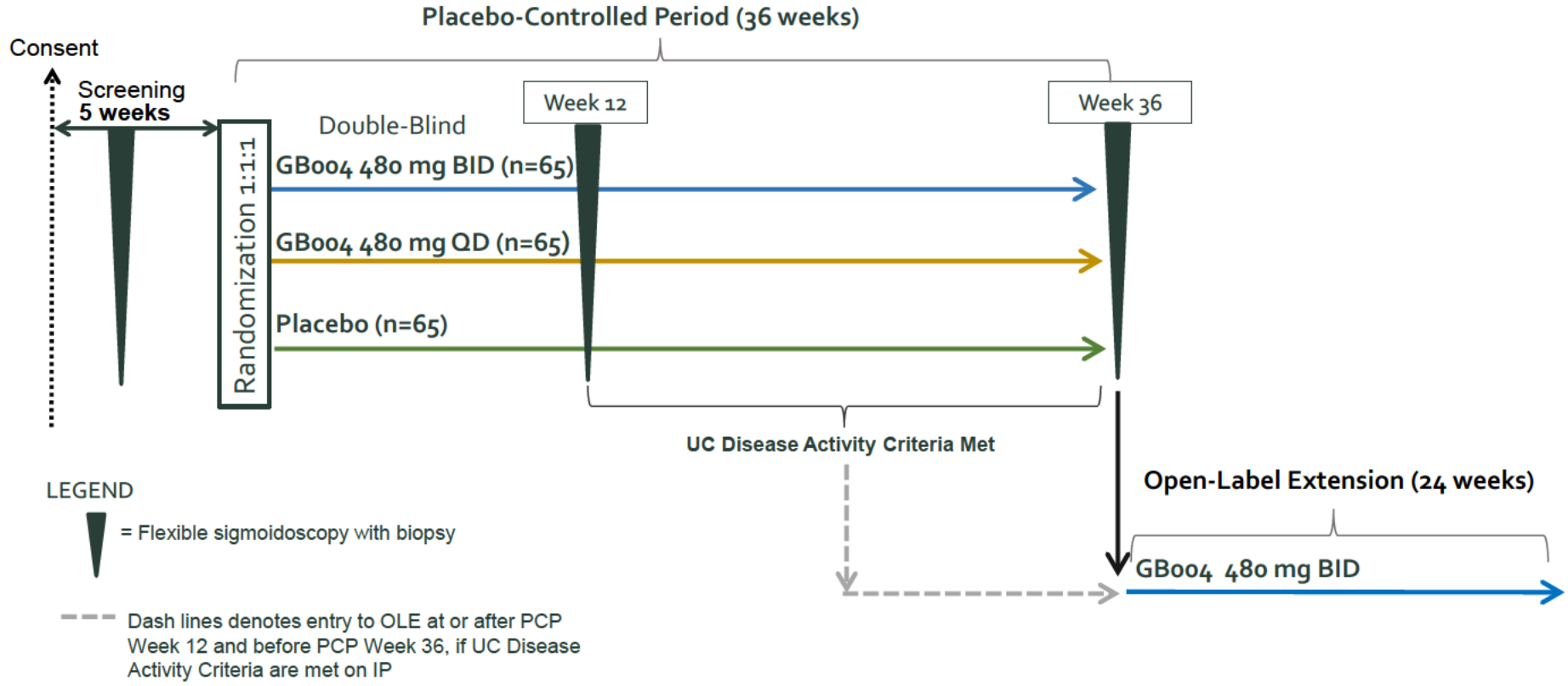
Duration

Total duration for study participation per subject is as follows:

Study period	PCP	OLE
Screening period:	up to 5 weeks	Not applicable
Treatment period:	up to 36 weeks	24 weeks
Follow-up period:	4 weeks after last dose of IP	

Data Review Committee: Yes

1.2. Study Schema



BID, twice per day; IP, investigational product; PCP, placebo-controlled period; QD, once daily; UC, ulcerative colitis

1.3. Schedule of Activities (SoA)

1.3.1. Placebo-Controlled Period – Schedule of Activities

PCP **Procedure**	**Screening**	**Treatment Period (Placebo-Controlled)**						**Unscheduled UC Disease Activity Criteria Assessment visit (post Week 12 Visit)**	**Early Discontinuation of IP OR Early Withdrawal from Study**	**Follow-up (+4 weeks after last dose of IP)**	Notes Some visits/study procedures may be done via virtual visits or at home visits. Refer to Appendix 9 and the Study Reference Manuals for more details on guidance for global health emergencies.
Visit **Week**	**1** -5 to -1	**2** **0** **(D1)**	**3** **2**	**4, 5** **4, 8**	**6** **12**	**7, 8, 9** **18, 24, 30**	**10** **36**	**If needed**	**If needed**		
Window (days)			**±2**	**±3**	**±5**	**±5**	**±5**			**-3/+7**	
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Medical history	X										
Smoking history	X										
Ulcerative colitis history	X										
Hematology with differential	X	X	X	X	X	X	X	X	X	X	See Appendix 2 for details.
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	See Appendix 2 for details. Note, inclusive of CRP.
Blood for serum markers		X			X		X	X	X	X	Collected predose (morning) Serum markers include, but not limited to: iron, transferrin, total iron binding capacity, serum ferritin, hepcidin, zinc
Blood for plasma markers	X			Wk 4 only	X		X	X	X	X	Collected predose (morning) on dosing days: EPO and VEGF
INR	X										See Appendix 2 for details.
Urinalysis	X				X		X	X	X	X	See Appendix 2 for details.

PCP **Procedure**	**Screening**	**Treatment Period (Placebo-Controlled)**						**Unscheduled UC Disease Activity Criteria Assessment visit (post Week 12 Visit)**	**Early Discontinuation of IP OR Early Withdrawal from Study**	**Follow-up (+4 weeks after last dose of IP)**	Notes Some visits/study procedures may be done via virtual visits or at home visits. Refer to Appendix 9 and the Study Reference Manuals for more details on guidance for global health emergencies.
Visit	**1**	**2**	**3**	**4, 5**	**6**	**7, 8, 9**	**10**	**If needed**	**If needed**		
Week	**-5 to -1**	**0 (D1)**	**2**	**4, 8**	**12**	**18, 24, 30**	**36**				
Window (days)			**±2**	**±3**	**±5**	**±5**	**±5**			**-3/+7**	
Serology	X										See Appendix 2 for details.
Pregnancy Test	S	U		U	U	U Monthly[a]	U	U	U	U	Serum pregnancy test (S) Urine pregnancy test (U) **a**. with a provided at-home urine pregnancy kit to be done in between clinic visits; if urine test is positive, subject must discontinue IP and return for confirmatory serum pregnancy test.
C Difficile/Stool pathogen, ova and parasites	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events	<==========X==========									==========>	See Section 8.3.
Complete physical exam	X										See Section 8.2.1
Vital Signs	X	X	X	X	X	X	X	X	X	X	See Section 8.2.2 for details. Includes height (screening) and weight
12-lead electrocardiogram	X				X		X		X	X	See Section 8.2.3 for details.

PCP **Procedure**	**Screening**	**Treatment Period (Placebo-Controlled)**						**Unscheduled UC Disease Activity Criteria Assessment visit (post Week 12 Visit)**	**Early Discontinuation of IP OR Early Withdrawal from Study**	**Follow-up (+4 weeks after last dose of IP)**	Notes Some visits/study procedures may be done via virtual visits or at home visits. Refer to Appendix 9 and the Study Reference Manuals for more details on guidance for global health emergencies.
Visit	**1**	**2**	**3**	**4, 5**	**6**	**7, 8, 9**	**10**	**If needed**	**If needed**		
Week	**-5 to -1**	**0 (D1)**	**2**	**4, 8**	**12**	**18, 24, 30**	**36**				
Window (days)			**±2**	**±3**	**±5**	**±5**	**±5**			**-3/+7**	
Flexible sigmoidoscopy with biopsy	X[b]				X[c]		X[c]	X[d]	X[d]		**b.** Screening colonoscopy may be performed instead of flexible sigmoidoscopy if needed for surveillance. Flexible sigmoidoscopy or colonoscopy will occur within 21 days of PCP Day 1/Week 0. **c.** Flexible sigmoidoscopy should be conducted prior to the completion of the PCP Week 12 and PCP Week 36 visits to allow time for central reading. (Refer to Appendix 9 for guidance on global health emergencies accommodation for endoscopy at the Week 12 and Week 36 visits.) **d.** To be conducted only if prior flexible sigmoidoscopy / colonoscopy was conducted > 4 weeks before the UC Disease Activity Criteria Assessment visit or Early Withdrawal from Study visit (refer to Appendix 8)
Dispense electronic diary (eDiary)	X										

PCP **Procedure**	**Screening**	**Treatment Period (Placebo-Controlled)**						**Unscheduled UC Disease Activity Criteria Assessment visit (post Week 12 Visit)**	**Early Discontinuation of IP OR Early Withdrawal from Study**	**Follow-up (+4 weeks after last dose of IP)**	Notes Some visits/study procedures may be done via virtual visits or at home visits. Refer to Appendix 9 and the Study Reference Manuals for more details on guidance for global health emergencies.
Visit	**1**	**2**	**3**	**4, 5**	**6**	**7, 8, 9**	**10**	**If needed**	**If needed**		
Week	**-5 to -1**	**0 (D1)**	**2**	**4, 8**	**12**	**18, 24, 30**	**36**				
Window (days)			**±2**	**±3**	**±5**	**±5**	**±5**			**-3/+7**	
Review eDiary		X	X	X	X	X	X	X	X		
Assess UC Disease Activity					X	X		X			Refer to Section 5.3, can also be evaluated at Unscheduled UC Disease Activity Criteria Assessment visit (if not during an already scheduled visit), if clinically indicated.
Review Mayo score, centrally read Endoscopic subscore, Rectal bleeding subscore, and Stool frequency score		X[e]			X		X	X			**e.** To be reviewed prior to randomization.
Physician's Global Assessment (PGA)	X	X	X	X	X	X	X	X	X	X	
Blood plasma sample (PK)		X[f]		Wk 4 only[f]	X[f]			X[g]	X[g]		**f.** Blood samples will be collected predose, and 0.5, 2, and 4 hours postdose. Timepoints are in reference to the **morning** dose. **g.** Only 1 sample will be collected.

PCP **Procedure**	**Screening**	**Treatment Period (Placebo-Controlled)**						**Unscheduled UC Disease Activity Criteria Assessment visit (post Week 12 Visit)**	**Early Discontinuation of IP OR Early Withdrawal from Study**	**Follow-up (+4 weeks after last dose of IP)**	Notes Some visits/study procedures may be done via virtual visits or at home visits. Refer to Appendix 9 and the Study Reference Manuals for more details on guidance for global health emergencies.
Visit	**1**	**2**	**3**	**4, 5**	**6**	**7, 8, 9**	**10**	**If needed**	**If needed**		
Week	**-5 to -1**	**0 (D1)**	**2**	**4, 8**	**12**	**18, 24, 30**	**36**				
Window (days)			**±2**	**±3**	**±5**	**±5**	**±5**			**-3/+7**	
Blood sample (PD)		X[h]	X[h]	X[h]	X[h]				X		**h.** Blood samples will be collected as follows: two (pre vs post dose) as EDTA plasma and two (pre vs post dose) as PaxGene. See Laboratory Manual for PD blood sample details. All timepoints are in reference to the **morning** dose.
Stool sample (PK and/or PD)	X				X		X	X	X		
Whole blood sample (PGx)		X[i]									**i.** Sample should be collected at Day 1/Week 0, but may instead be collected at any subsequent visit. Collect predose (**morning**)
Randomization		X									
Dispense IP		X	X	X	X	X					
Collect unused IP, conduct accountability and review dosing compliance			X	X	X	X	X	X	X[j]		j. Only required at Early Discontinuation of IP visit

Abbreviations: CRP, c-reactive protein; D, day; EDTA, ethylenediaminetetraacetic acid; EPO, erythropoietin; INR, international normalized ratio; IP, investigational product; IRT, interactive response technology; PCP, Placebo-Controlled period; PD, pharmacodynamic(s); PGx, pharmacogenetic(s); PK, pharmacokinetic(s); VEGF, vascular endothelial growth factor; Wk, week.

1.3.2. Open-Label Extension - Schedule of Activities

OLE Procedure	OLE Enrollment visit (same as PCP last visit)*	Treatment Period		End of OLE / ET	Follow-up (+4 weeks after last dose of IP)	Notes *Assessments completed within 14 days of PCP last visit will not be required to be repeated during the OLE Enrollment visit
Visit	**201**	**202**	**203, 204, 205, 206,**	**207**	**208**	Some visits/study procedures may be done via virtual visits or at home visits. Refer to Appendix 9 and the Study Reference Manual for more details on guidance for global health emergencies.
OLE Week	**0/D1**	**2**	**4, 8, 12, 18**	**24**	**+ 4 weeks from End of OLE/ET**	
Window (days)		**±3**	**±3**	**±3**	**±3**	
Hematology with differential	X	X	X	X	X	See Appendix 2 for details.
Clinical chemistry	X	X	X	X	X	See Appendix 2 for details. Note, inclusive of CRP.
Urinalysis	X			X	X	See Appendix 2 for details.
Pregnancy test	X		U Monthly[a]	S	S	Serum (S), Urine (U) **a**. with a provided at-home urine pregnancy kit to be done in between clinic visits; if urine test is positive, subject must discontinue IP and return for confirmatory serum pregnancy test.
Concomitant medications	X	X	X	X	X	
Adverse events	<==========X==========				==========>	
Complete physical exam				X		Refer to Section 8.2.1
Vital Signs	X	X	X	X	X	Includes weight
12-lead electrocardiogram			Week 12	X	X	
Review eDiary		X	X	X		
Physician's Global Assessment (PGA)	X	X	X	X	X	
Blood for serum markers	X		Week 12	X		Collected predose (morning) Serum markers include, but not limited to: iron, transferrin, total iron binding capacity, serum ferritin, hepcidin, zinc
Blood for plasma markers	X		Week 12	X		Collected predose (morning) on dosing days: EPO and VEGF

OLE **Procedure**	**OLE Enrollment visit (same as PCP last visit)***	**Treatment Period**		**End of OLE / ET**	**Follow-up (+4 weeks after last dose of IP)**	**Notes** *Assessments completed within 14 days of PCP last visit will not be required to be repeated during the OLE Enrollment visit
Visit	**201**	**202**	**203, 204, 205, 206,**	**207**	**208**	Some visits/study procedures may be done via virtual visits or at home visits. Refer to Appendix 9 and the Study Reference Manual for more details on guidance for global health emergencies.
OLE Week	**0/D1**	**2**	**4, 8, 12, 18**	**24**	**+ 4 weeks from End of OLE/ET**	
Window (days)		**±3**	**±3**	**±3**	**±3**	
PK blood sample		X[b]				**b.** PK samples to be collected at predose, 0.5, 2 and 4 hours postdose
Stool sample (PD)	X			X		See Section 8.5 for details
Dispense IP	X	X	X			
Collect unused IP, conduct accountability and review dosing compliance		X	X	X		

Abbreviations: CRP, c-reactive protein; D, day; ET, Early termination; EPO, erythropoietin; IP, investigational product; OLE, Open-Label extension; PCP, Placebo-Controlled period; PD, pharmacodynamic(s); PK, pharmacokinetic(s); VEGF, vascular endothelial growth factor.

2. INTRODUCTION

2.1. Study Rationale

GB004 (formerly AKB-4924) is a novel small molecule in development for the treatment of inflammatory bowel disease (IBD). The novel approach of GB004 is based on evidence that hypoxia inducible factor 1 alpha (HIF-1α), a member of the hypoxia inducible factor (HIF) transcription factor family, has a crucial role in the maintenance of epithelial barrier integrity and in the modulation of the innate inflammatory response in mouse models of IBD.

Small molecule prolyl hydroxylase inhibitors (PHDi's) stabilize HIF-1α protein and have shown efficacy in multiple mouse models of IBD that include trinitrobenzene sulfonic acid (TNBS) and dextran sulfate sodium (DSS)-induced colitis models and the tumor necrosis factor alpha (TNFα)-driven terminal ileitis model (Ablin, 1999; Minaiyan, 2012). Prolyl hydroxylases (PHDs) are key regulators of the HIF pathway (Eltzschig, 2014). These findings support PHD inhibition as a target for treating ulcerative colitis (UC).

GB004, a HIF-1α stabilizer, is being developed as an oral therapeutic, gut-targeted treatment for UC with higher intestinal than systemic exposure. The relatively low oral bioavailability (< 20%) and preferential distribution to the gastrointestinal (GI) tissues observed in nonclinical studies, combined with its mechanism of action in gut lumen and positive effects on gut healing and inflammation in animal models of colitis, provide rationale for further development in human subjects.

GB004 has been shown in studies of both healthy volunteers (AKB-4924-CI-1001, AKB-4924-CI-1002, and GB004-1902) and patients with UC (GB004-1101) to be a gut-targeted treatment with higher intestinal than systemic exposure. In addition, the GB004-1101 study, although limited by only 4 weeks of dosing, showed trends in improvement in clinical and histologic outcomes in UC patients. GB004, Inc. has developed tablet formulations with 2 release profiles, tablets and delayed-release (DR) tablets, which have distinct systemic profiles with both delivering GB004 to the colonic tissue.

This 2-part study, comprising of a 36-week placebo-controlled period and a 24-week open-label extension period, will assess the efficacy and safety of GB004 when added to background UC therapy of 5-aminosalicylate (5-ASA) with or without systemic steroids.

2.2. Background

UC is the result of an unrelenting, severe inflammatory response mounted against an environmental trigger in a genetically susceptible host. The inflammatory response, in turn, causes a breach in intestinal barrier integrity which allows influx of luminal antigens setting up a vicious cycle of inflammation and epithelial injury that perpetuates the disease process.

UC symptoms include rectal bleeding and diarrhea (Schroeder, 1987). Consistently, UC is associated with a significantly reduced quality of life and recent data indicate increased mortality especially among patients diagnosed at early ages. Despite the improved efficacy of UC treatment with anti-tumor necrosis factor (anti-TNF) agents and anti-integrin agents (eg, vedolizumab), there remains a large subset of patients who either do not respond adequately to conventional

therapy or biologic therapy and do not achieve long-term remission. Perhaps the best indicator of the inadequacy of current therapy is that surgery is required for about 23-46% of patients with UC (Shen, 2008). Considering the worldwide increase in UC, novel approaches to managing UC are urgently needed. (Bernstein, 2012; Kaplan, 2012; Singh, 2015).

The overall goal of treatment for patients with active UC is to induce and maintain remission and to induce and maintain mucosal healing (de Mattos, 2015; Heyman, 2005; Jain, 2019; Lamb, 2019; Ng, 2009; Singh, 2019). Treatment of UC consists of anti-inflammatory and immunosuppressive therapies that are chosen to maximize efficacy while avoiding toxicity. The therapy chosen is therefore dependent on the patient's disease severity and their response to therapy (Jain, 2019; Kelsen, 2020; Ko, 2019; Kornbluth, 2010; Ng, 2009). While agents used to treat mild to moderate UC are generally well tolerated, as the severity of UC increases, so do the potential toxicities of the medications required to manage the disease. In mild to moderate UC patients unresponsive to local therapy or in patients with more severe or more extensive disease, systemic treatment with an oral 5-ASA, such as mesalamine, olsalazine, sulfasalazine, and balsalazide, is commonly required (Jain, 2019; Ng, 2009; Turner, 2011; Whaley, 2019). After patients fail 5-ASA therapy, the next recommended add-on therapy is oral systemic or locally acting steroids (Ko, 2019). While >90% of UC patients in population-based cohorts receive 5-ASA therapy within 1 year of diagnosis, 50% will also be prescribed steroids during the course of their disease (Singh, 2019). Therapies indicated for moderate to severe UC after steroids are either oral immunomodulators or biologics. These therapies are associated with higher rates of clinical remission, but also with higher risk of adverse events such as infection or malignancy (Kirchgesner, 2018). Biologics are typically employed after the failure of 5-ASAs due to the associated risks of these therapies, lack of durable response due to immunogenicity, and requirement of parental administration. There is an ongoing unmet medical need for an oral UC treatment that is highly effective in achieving long-term remission and mucosal healing with limited side effects in these patients with 5-ASA failure and prior to biologics (Levesque, 2015). GB004, a HIF-1α stabilizer, is being developed as an oral therapeutic, gut-targeted treatment for UC. The GB004 mechanism of action in gut lumen, positive effects on gut healing and inflammation in animal models of colitis, trends in improvement in disease related outcomes such as histologic remission, mucosal healing, rectal bleeding, and safety and tolerability results over 4 weeks of treatment in the Phase 1b GB004-1101 study, provide rationale for further development of GB004 in UC subjects.

2.3. Benefit/Risk Assessment

More detailed safety findings from completed and ongoing studies may be found in the Investigator's Brochure (IB).

2.3.1. Benefit Assessments

Development of GB004 for UC is supported by its mechanism of action, which stabilized HIF-1α in Phase 1, and the evidence that GB004 show enhanced healing and decreased inflammation in animal models of colitis.

The potential benefits of GB004 treatment for subjects in this study were shown in the GB004-1101 Phase 1b Study and included trends in improvement with GB004 compared to placebo in histologic remission, rectal bleeding, and mucosal healing; however, the study was limited by the 28 days of dosing and small sample size. This longer Phase 2 clinical study is designed to evaluate the impact of GB004 on these efficacy endpoints and provide sufficient time for the initial improvement of the clinical signs and symptoms of ulcerative colitis, and then the longer-term impact on clinical remission and mucosal healing. This study will also allow for subjects in the PCP to transition to OLE at or after PCP Week 12 and before PCP Week 36 and receive GB004 480 mg BID if they meet the predefined UC disease activity criteria (Section 5.3).

2.3.2. Risk Assessments

As of May 27, 2020, a total of 117 subjects, comprising 94 healthy volunteers and 23 subjects with active UC, have received GB004. GB004 Powder for Oral Solution has been studied in healthy volunteers receiving single and multiple doses up to 240 mg daily for 8 days (AKB-4924-CI-1001 and AKB-4924-CI-1002) and in subjects with active UC receiving 120 mg daily for 28 days (GB004-1101). GB004 formulations (Powder for Oral Solution and tablets) have been studied in healthy volunteers receiving doses up to 240 mg daily for 7 days (GB004-1902). There are no identified risks of GB004. There are 2 potential risks of GB004.

These potential risks are:

- Nausea: The overall incidence of nausea was 18.8% (22/117) in GB004-treated subjects versus none in placebo-treated subjects. Nausea in GB004-treated subjects was generally characterized as: mild, occurring more frequently with GB004 doses of 120 mg or greater, first occurring within the first hour after the first dose and lasting 1 day, without concurrent vomiting, and of low clinical impact with infrequent discontinuations of GB004 (1 subject).
- Dizziness: The overall incidence of dizziness was 11.1% (13/117) in GB004-treated subjects versus 4.9% (2/41) in placebo-treated subjects. Dizziness in GB004-treated subjects was generally characterized as: mild, occurred more frequently with GB004 doses of 120 mg or greater, first occurring within 1 day after first dose and lasting 1 day, without impairment of function, and with no discontinuation of GB004.

Preliminary safety results from the study of GB004 tablet formulations (GB004-1902) show that nausea and dizziness were reported less frequently than were previously reported with the solution formulation. GB004 formulations have been studied in a Phase 1 study (GB004-1902) in healthy volunteers receiving daily doses of 120 mg solution or placebo, or up to 240 mg tablet,

delayed-release tablet, or placebo for 7 days. Overall, TEAEs were reported by 9 of 32 (28%) subjects who received GB004 and 3 of 10 (30%) subjects who received placebo. All TEAEs were mild in severity. TEAEs reported in more than one subject in the GB004 group included nausea (9% GB004; none in placebo), headache (9% GB004; 10% placebo), diarrhea (6% GB004; 20% placebo), and liver function test elevation (6% GB004; none in placebo). Preliminary safety results from this study suggest that GB004 formulations of 120 mg solution and up to 240 mg tablet, and 240 mg DR tablet are generally well tolerated in healthy subjects.

GB004 Powder for Oral Solution has been studied in subjects with active UC receiving daily doses of 120 mg in a Phase 1b study (GB004-1101). The majority of adverse events (AEs) were reported as Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2 in severity and were considered not related. The most common (≥ 10%) TEAEs reported in GB004-treated subjects included nausea (21.7% GB004; 0% placebo) and dysgeusia (13% GB004; 0% placebo). Preliminary results suggest that GB004 Powder for Oral Solution 120 mg daily is generally well tolerated in subjects with active UC.

2.3.3. Overall Benefit and Risk Conclusion

Given the potential benefits for subjects and the potential benefit of identifying a new therapeutic for UC and the potential risks of GB004, the benefit versus risk ratio for GB004 is considered favorable.

3. OBJECTIVES AND ENDPOINTS

3.1. Placebo-Controlled Period Objectives and Endpoints

Objectives	Endpoints (see definitions for efficacy endpoints in Section 3.3)
Primary	
• To evaluate the effect of GB004 compared to placebo on clinical remission at PCP Week 12	• Proportion of subjects with clinical remission at PCP Week 12, defined as a Modified Mayo score ≤ 2, with a Rectal bleeding subscore of 0, Stool frequency subscore of 0 or 1 (with a ≥ 1 point decrease from baseline), and Endoscopic subscore of 0 or 1
Secondary	
• To evaluate the effect of GB004 on clinical response, histologic remission, endoscopic improvement and mucosal healing at PCP Week 12	• Proportion of subjects with clinical response at PCP Week 12, defined as reduction in the Modified Mayo score of ≥ 2 points and ≥ 35 percent reduction from baseline, including a decrease in Rectal bleeding subscore of ≥1 or absolute Rectal bleeding subscore of ≤ 1 • Proportion of subjects with histologic remission at PCP Week 12, defined as Robarts Histopathology Index (RHI) ≤ 3 with lamina propria neutrophils subscore = 0 and neutrophils in epithelium subscore = 0 • Proportion of subjects with endoscopic improvement at PCP Week 12, defined as endoscopic subscore of 0 or 1 • Proportion of subjects with mucosal healing at PCP Week 12, defined as endoscopic improvement and histologic remission
• To evaluate the effect of GB004 on clinical remission, clinical response, histologic remission, endoscopic improvement, and mucosal healing at PCP Week 36	• Proportion of subjects with clinical remission at PCP Week 36 • Proportion of subjects with clinical response at PCP Week 36 • Proportion of subjects with histologic remission at PCP Week 36 • Proportion of subjects with endoscopic improvement at PCP Week 36

Objectives	Endpoints (see definitions for efficacy endpoints in Section 3.3)
	• Proportion of subjects with mucosal healing at PCP Week 36
Safety	
• To evaluate the safety and tolerability of GB004	• Incidence of treatment emergent adverse events (TEAEs)
Exploratory	
• To evaluate other safety outcomes	• Change from Baseline in laboratory, vital signs, and electrocardiogram (ECG) parameters
• To explore other measures of the effect of GB004 on disease activity over time	• Proportion of subjects with resolution of Rectal bleeding • Proportion of subjects with histologic response • Proportion of subjects with Geboes score ≤ 2 • Proportion of subjects with steroid-free clinical remission at PCP Week 36 • Proportion of subjects with clinical remission by Mayo score and resolution of rectal bleeding • Proportion of subjects with clinical remission by Mayo score • Proportion of subjects with clinical response by Mayo score • Proportion of subjects with Modified Mayo score of ≤ 2, with no individual subscore > 1 • Proportion of subjects with disease clearance • Proportion of subjects with symptomatic remission • Proportion of subjects with modified symptomatic remission • Proportion of subjects with Partial Mayo remission • Proportion of subjects with reduction of ≥ 2 points from baseline in partial Mayo score

Objectives	Endpoints (see definitions for efficacy endpoints in Section 3.3)
	• Proportion of subjects with a 6-point Mayo score clinical remission • Change from Baseline in Modified Mayo score • Change from Baseline in Mayo score • Change from Baseline in Partial Mayo score over time • Change from Baseline in Mayo subscores over time • Change from Baseline in RHI score • Change from Baseline in the UC-100 Index
• To explore the PK of GB004	• Plasma and colon tissue concentrations of GB004
• To explore target engagement (TE) and pharmacodynamic (PD) response	• Change from baseline in tissue and blood markers of target engagement, eg, HIF-1α, EGLN1-2-3, etc. • Change from baseline in markers of pharmacodynamics, eg, fecal calprotectin, fecal lactoferrin, and neutrophil activity (myeloperoxidase) • Change from baseline in tissue, blood, and stool in downstream genes and proteins, eg, CAIX, MPO, c-reactive protein (CRP), TJP, CLDN1, etc. as a function of exposure (C_{max}, T_{max}, AUC), efficacy endpoints (eg, clinical remission, clinical response), and/or safety endpoints
• To explore baseline markers with response to treatment with GB004	• Relationship between tissue, blood, and stool baseline markers (eg, HIF-1α, EGLN1-2-3, calprotectin, etc.) and response to treatment, as measured by efficacy endpoints (eg, clinical remission, clinical response), and/or safety endpoints
• To explore pharmacogenetics (PGx)	• Effect of naturally occurring genetic variation on the efficacy (eg, clinical remission, clinical response), safety, and/or PK profile (C_{max}, T_{max},

Objectives	Endpoints (see definitions for efficacy endpoints in Section 3.3)
	AUC) and tissue concentrations associated with treatment with GB004

3.2. Open-Label Extension (OLE) Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GB004	• Incidence of TEAEs
Exploratory	
• To evaluate other safety outcomes	• Change from GB004 baseline in laboratory, vital signs, and ECG parameters
• To explore measures of the effect of GB004 on disease activity over time	• Proportion of subjects with resolution of Rectal bleeding at OLE Week 24 • Proportion of subjects with partial Mayo score of ≤2 with no individual subscore >1 over time • Proportion of subjects with reduction of ≥2 points from GB004 baseline in partial Mayo score over time • Change from GB004 baseline in partial Mayo score over time • Proportion of subjects with a 6-point Mayo score clinical remission at OLE Week 24
• To explore PD response	• Change from GB004 baseline in fecal calprotectin • Change from GB004 baseline in blood, and stool in downstream markers, included but not limited to CRP

3.3. Efficacy Endpoint Definitions

Table 2: Efficacy Endpoint Definitions

Note: For the purposes of the endpoint definitions, refer to Section 9.4 for baseline definitions.

Endpoint	Definitions
Clinical remission	Modified Mayo score ≤ 2, with a Rectal bleeding subscore of 0, Stool frequency subscore of 0 or 1 (with ≥1 point decrease from baseline), and Endoscopic subscore of 0 or 1 (refer to Section 8.1.2 for Modified Mayo score)
Clinical response	Reduction in the Modified Mayo score of ≥ 2 points and ≥ 35% from baseline, including a decrease in Rectal bleeding subscore of ≥1 or absolute Rectal bleeding subscore of ≤ 1
Histologic remission	RHI ≤ 3 with lamina propria neutrophils subscore = 0 and neutrophils in epithelium subscore = 0 (refer to Section 8.1.3)
Endoscopic improvement	Endoscopic subscore 0 or 1
Mucosal healing	Endoscopic improvement and histologic remission
Resolution of Rectal bleeding	Rectal bleeding subscore = 0
Histologic response	Decrease from baseline in RHI of ≥ 7 (refer to Section 8.1.3)
Steroid-free remission	Clinical remission with no systemic corticosteroid use among subjects who were using systemic corticosteroids at baseline
Clinical remission by Mayo score	Mayo score ≤ 2, with no Mayo individual subscores >1 (refer to Section 8.1.2 for Mayo score)
Clinical response by Mayo score	Reduction in the Mayo score of ≥ 3 points and ≥ 30% from baseline, including a decrease in Rectal bleeding subscore of ≥ 1 or absolute Rectal bleeding subscore of ≤1
Disease clearance	Clinical remission and histologic remission (Danese, 2020)
Symptomatic remission	Mayo score of ≤ 2, with no individual subscore > 1 and both Rectal bleeding and Stool frequency subscores of 0
Modified symptomatic remission	Endoscopic improvement, resolution of Rectal bleeding and Stool frequency subscore of 0
Partial Mayo remission	Partial Mayo score of ≤ 2 with no individual subscore >1 (refer to Section 8.1.2 for partial Mayo score)
6-point Mayo score clinical remission	6- point Mayo score < 2 with a Rectal bleeding subscore of 0 and Stool frequency subscore of 0 or 1 (with ≥ 1 point decrease from baseline) (Lewis, 2008) (refer to Section 8.1.2 for 6-point Mayo score)

Abbreviations: RHI, Robarts Histopathology Index.

4. STUDY DESIGN

4.1. Overall Study Design

This is a 2-part study in adult subjects with mild-to-moderate active UC who have disease activity despite treatment with 5-ASA with or without systemic steroids:

- The Placebo-Controlled period (PCP) is a randomized, placebo-controlled, multi-center, 36-week study evaluating the efficacy, safety, tolerability and pharmacokinetics (PK) of 2 dose regimens of GB004; the initial 12 weeks of treatment will be double-blind
- The OLE is an open-label, multi-center, 24-week study evaluating the safety and tolerability of GB004 twice per day (BID) dose regimen

Subjects who complete the Week 36 visit on IP and subjects who meet the predefined UC Disease Activity criteria at or after PCP Week 12 visit and prior to PCP Week 36 visit on IP can enter the OLE (for details refer to Section 5.3).

All subjects participating in the study will be required to maintain a stable dose of 5-ASA throughout the study. Subjects on systemic corticosteroids must remain on a stable dose during the initial 12 weeks of the PCP (for details refer to Section 6.5.2). After the PCP Week 12 visit, a standardized taper from systemic corticosteroids may be attempted at any time.

All subjects will attend a Follow-up visit at the clinic 4 weeks after last dose of IP.

A data review committee (DRC) will periodically convene to review unblinded overall safety and emerging efficacy results (Section 9.5.1).

A schematic of the study design is presented in Section 1.2.

4.1.1. Placebo-Controlled Period (36 weeks)

After signing an informed consent form (ICF), subjects will be screened for study eligibility over a Screening period of up to 5 weeks. During the Screening period, subjects will capture stool frequency and rectal bleeding symptoms in a provided electronic diary (eDiary) on a daily basis. Flexible sigmoidoscopy or colonoscopy will be performed at screening. Subjects not meeting the eligibility criteria will be deemed screen failures and will not continue participation in the study.

On Day 1/Week 0, eligible subjects will be randomized 1:1:1 to receive the following treatments for 36 weeks:

- GB004 480 mg BID
- GB004 480 mg once daily (QD)
- Placebo

Randomization will be stratified by systemic corticosteroid use at baseline (yes/no).

All subjects will dose investigational product (IP) BID to maintain the blind (for details refer to Section 6.1). The first dose of IP will be administered in the clinic on Day 1/Week 0 with food. All subsequent doses will be taken at home with food, with the exception of the morning doses at

the Week 2, 4, 8, 12, and 36 visits where IP will be administered in the clinic, with food, after predose blood collection as specified in the Schedule of Activities (SoA) in Section 1.3.1 – PCP.

After initiation of IP on Day 1/Week 0, subjects will return to the clinic and will be evaluated as specified in the SoA, see Section 1.3.1. A flexible sigmoidoscopy with biopsies will be performed at the PCP Week 12 and Week 36 visits (and at the Unscheduled UC Disease Activity Criteria Assessment visit(s) and at the Early Withdrawal from Study visit, if applicable).

Subjects who permanently discontinue IP without enrolling in the OLE will be encouraged to continue in the PCP and will complete the Early Discontinuation of IP visit at the time of IP discontinuation and then complete the remaining PCP study visits per the SoA. At subsequent visits, all study procedures will be completed per the SoA excluding dispensation/return and accountability of IP.

Subjects who withdraw from the PCP without enrolling in the OLE, regardless of the reason, will be requested to return to the clinic to complete the Early Withdrawal from Study visit and will be asked to return for a Follow-up visit approximately 4 weeks after their last dose of IP to assess safety.

For dose modifications refer to Section 6.5.1.

4.1.2. OLE (24 weeks)

Subjects may participate in the 24-week OLE if in the opinion of the Investigator they have been compliant with study procedures and:

- Completed the Week 36 visit on IP; or
- Met the predefined UC Disease Activity criteria any time after PCP Week 12 visit and prior to PCP Week 36 visit on IP (refer to Section 5.3)

Beginning at the OLE Enrollment visit, all subjects will receive GB004 480 mg BID for 24 weeks. All doses will be taken at home with food with the exception of the morning dose at the OLE Enrollment visit (if last dose of PCP IP has not been taken earlier in the day), OLE Week 2, 12 and End of OLE visit/Early termination (ET) visit where IP will be administered in the clinic, with food, after predose blood collection as specified in the SoA (Section 1.3.2 – OLE). Subsequently, subjects will return to the clinic and be evaluated as specified in the SoA (Section 1.3.2 - OLE).

Consideration should be given to discontinuing IP for subjects who do not show clinical improvement per Investigator's judgement by OLE Week 12. Subjects who permanently discontinue IP during the OLE will be withdrawn from the study, complete the End of OLE/ET visit and will be asked to return for a Follow-up visit approximately 4 weeks after their last dose of IP to assess safety.

4.2. Scientific Rationale for Study Design

The PCP is designed as a randomized, placebo-controlled study to evaluate the efficacy and safety of 2 dose regimens of GB004 relative to placebo over a 36-week treatment period. The first 12 weeks will be double-blind.

The OLE is designed to primarily evaluate the safety and tolerability of GB004 BID over a 24-week treatment period and allows subjects who originally were assigned to placebo in the PCP to have an opportunity to be treated with GB004.

4.2.1. Study Population

The target population is adult subjects with mild-to-moderate active UC and have disease activity despite treatment with 5-ASA with or without prednisone (or equivalent), beclomethasone, budesonide, or budesonide-MMX. Mild-to-moderate active UC will be defined as a Mayo score of 5-10, inclusive, with an Endoscopic subscore of ≥ 2, a Stool frequency subscore ≥ 1, and a Rectal bleeding subscore ≥ 1.

4.2.2. Endpoint Selection

Clinical remission has been chosen as the primary endpoint based on its clinical and regulatory importance in UC and the GB004 mechanism of action, which may lead to restoration of epithelial barrier function and resolution of inflammation and symptoms. This Phase 2 study is designed to evaluate the impact of GB004 on a set of efficacy endpoints while allowing sufficient time for the initial improvement of the clinical signs and symptoms of UC. Safety will be evaluated throughout with AE monitoring and other safety assessments.

4.2.3. Placebo Rationale

The study will compare the impact of adding GB004 versus placebo to background therapy for UC. Placebo will be used as a comparator to assess any differences in treatment effect or perception of response due to participation in the study. A placebo-controlled design is necessary because UC is a disease that waxes and wanes over time and is measured by endpoints with subjective components. It is important to be able to differentiate the biological activity of GB004 compared to the "placebo effect," which may be as high as 15 to 20% depending on the endpoint chosen. Comparisons between the GB004 and placebo treatment groups will facilitate differentiation of the GB004 safety profile from that of the background UC therapy.

4.3. Justification for Dose

Phase 1 studies have shown GB004 to be a gut-targeted treatment with higher intestinal than systemic exposure with trends in improvement in histologic remission, rectal bleeding, and mucosal healing in subjects with UC. The previous Phase 1b study in subjects with UC (GB004-1101) was limited by 4 weeks of dosing with a low dose (GB004 Powder for Oral Solution 120 mg QD) and by the number of subjects evaluated. Colonic concentrations were variable but frequently below target concentrations based on efficacy predictions from nonclinical animal models of colitis. Therefore, higher doses (480 mg QD and 480 mg BID) are planned in this Phase 2 study (refer to study schema in Section 1.2). This Phase 2 study is designed to evaluate the impact of GB004 on a set of efficacy endpoints while allowing sufficient time for the initial improvement of the clinical signs and symptoms of ulcerative colitis, and then to assess (at 36 weeks) the longer term impact on clinical remission and mucosal healing.

The PCP will evaluate 2 dose regimens of GB004, 480 mg (240 mg GB004 tablets and 240 mg GB004 DR tablets) administered BID or QD, compared to placebo. Subjects will be dosed under

fed conditions. These doses and the longer treatment duration are supported by completed nonclinical toxicology and clinical studies based on the following considerations:

- Tolerability and safety profile of GB004 from the SAD and MAD studies, and evidence of target engagement from colon tissue biopsies from the MAD study.
- Preliminary tolerability, safety, PK profile with minimal observed accumulation of GB004 following QD dosing for 28 days, and trends in improvement in disease-related outcomes such as histologic remission and mucosal healing in the Phase 1b GB004-1101 study in subjects with active UC.
- Preliminary tolerability, safety, and PK profile of GB004 tablets and GB004 DR tablets in the Phase 1a GB004-1902 study in healthy male and female volunteers, which demonstrated tablet plasma exposures that enable dosing at the proposed Phase 2 dose levels with a combination of GB004 tablets and GB004 DR tablets. The maximum observed concentration at steady-state (C_{max}) and AUC_{last} of GB004 tablets were similar to those with GB004 Powder for Oral Solution. When subjects were given GB004 tablets when fed, steady-state C_{max} and AUC_{0-24} of GB004 appeared to be generally similar to subjects given GB004 tablets when fasted after normalization to dose. Given the rapid elimination of GB004 from systemic circulation, the steady-state C_{max} of GB004 following BID dosing is expected to be similar to that following QD dosing, while daily AUC are expected to double following BID dosing compared to QD dosing. GB004 DR tablets when given fasted had a lower C_{max} and AUC_{last} than GB004 tablets fasted or GB004 solution.

Based on the current safety and PK results with GB004 tablets at doses up to 240 mg, adequate safety margins of the projected human 480 mg GB004 (240 mg GB004 tablets and 240 mg GB004 DR tablets) BID treatment arm exposure values, and the selected doses taken with food, the proposed Phase 2 doses are expected to be tolerated.

The OLE will evaluate GB004 480 BID because this dose is expected to inform long-term safety of GB004 at doses at or below this maximum dose in the study.

The 9-month nonclinical toxicology results, and clinical safety, tolerability, PK and target engagement data, along with the preliminary evidence of clinical activity of GB004 in subjects with UC, support evaluating GB004 480 mg administered BID or QD under fed conditions for up to 60 weeks.

4.4. Study Duration

Total duration for study participation per subject is as follows:

Study period	PCP	OLE
Screening period:	up to 5 weeks	Not applicable
Treatment period:	up to 36 weeks	24 weeks
Follow-up period:	4 weeks after last dose of IP	

4.5. End of Study Definition

End of study is defined separately for the PCP and the OLE.

4.5.1. Placebo-Controlled Period

A subject will be regarded to have completed the PCP if he/she completes the PCP Week 36 visit. The end of the PCP is defined as the date of the last visit of the last subject in the PCP.

4.5.2. OLE

A subject will be regarded to have completed the OLE if he/she completes the OLE Week 24 visit. The end of OLE is defined as the date of the last OLE visit of the last subject in the OLE.

5. ELIGIBILITY CRITERIA

5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria are met:

Age and Sex

1. Adult male and female subjects aged ≥ 18 years (≥ 19 years in South Korea per country regulation/definition of adult) at the time of signing the informed consent form (ICF) prior to initiation of any study specific activities/procedures.

Type of Subject and Disease Characteristics:

2. UC diagnosed at least 3 months prior to first dose of IP on Day 1. The diagnosis should be confirmed by clinical and endoscopic evidence and corroborated by a histopathology report (note: the screening endoscopy and histopathology results may be used to confirm the diagnosis if no prior report is readily available).
3. Mayo score of 5-10, inclusive, with a centrally read Endoscopic subscore ≥ 2 and a Rectal bleeding subscore ≥ 1 and Stool frequency score ≥ 1.
4. Evidence of UC extending ≥ 15 cm from the anal verge as determined by screening flexible sigmoidoscopy or colonoscopy.

5. Colonoscopy within the past 2 years (or during the Screening period) to screen for dysplasia (unless otherwise recommended by local and national guidelines) if the subject has had UC for 8 or more years duration.

Allowed UC Therapy

6. Currently receiving treatment for UC, on a stable dose for at least 2 weeks prior to flexible sigmoidoscopy or colonoscopy, with oral 5-ASA (eg, mesalamine, sulfasalazine) alone or with one of the following oral treatments:
   a. prednisone ≤ 20 mg/day or equivalent or
   b. beclomethasone ≤ 5 mg/day or
   c. budesonide or budesonide multi-matrix (MMX) of ≤ 9 mg/day

Body Mass Index (BMI)

7. BMI 18 to 35 kg/m^2.

Pregnancy and Contraception

Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

8. Women meeting the definition of non-childbearing potential or women of childbearing potential must agree to the contraceptive guidance (see Appendix 4).
9. Men must agree to the contraceptive guidance (see Appendix 4).

Informed Consent

10. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Excluded Prior Therapy

1. Prior approved biologic therapy used for the treatment of UC.
2. Enemas or suppository formulations of steroids or 5-aminosalicylates within 2 weeks of screening flexible sigmoidoscopy/colonoscopy.
3. Tofacitinib, oral cyclosporine, sirolimus or mycophenolate mofetil within 8 weeks of Day 1.
4. Azathioprine, or 6-mercaptopurine within 1 day of Day 1.
5. Anti-diarrheal medications (e.g., loperamide, diphenoxylate/atropine) during screening.
6. Epoetin alfa within 8 weeks of Day 1.
7. Cholestyramine or other drugs interfering with enterohepatic circulation within 14 days of Day 1.

8. Chronic non-steroidal anti-inflammatory agents (NSAID) use (occasional use of NSAID, acetaminophen, or aspirin up to 325 mg/day is allowed).
9. Treatment with strong cytochrome P450 (CYP) 3A inhibitors and/or CYP3A inducers, and inhibitors of uridine-diphosphoglucuronosyl transferase (UGT) within 21 days or within 5 half-lives, whichever is longer, of the respective medication prior to Day 1 (see Appendix 6 for examples).

Medical Conditions

10. Diagnosis of Crohn's disease or indeterminate colitis, pouchitis.
11. Fulminant colitis, toxic megacolon, or in Investigator's judgement likely to require colectomy or ileostomy within 16 weeks of Day 1.
12. Stool sample positive for *Clostridium difficile* (*C difficile*) toxin, stool pathogens, or ova and parasites infection on screening laboratory tests. If positive, subjects may be treated and retested.
13. A current malignancy, current colonic dysplasia or previous history of cancer in remission for less than 5 years prior to screening. Subjects will not be excluded if they had localized carcinoma of the skin that was resected for cure, cervical dysplasia that has been adequately treated, or colonic dysplasia that has been completely removed.
14. Known pre-existing, unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices or persistent jaundice), cirrhosis, known biliary abnormalities, known pre-existing non-alcoholic steatohepatitis (NASH), or active infection with Hepatitis B or Hepatitis C.
15. Immunodeficiency, including that due to human immunodeficiency virus (HIV), other than that explained by systemic corticosteroid use.
16. Other concurrent medical conditions: known, pre-existing clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, cardiovascular, respiratory (eg, including active tuberculosis), hematological, or any other system abnormalities that are uncontrolled with standard treatment.
17. Any other medical condition or laboratory abnormality that, in the opinion of the Investigator, would prohibit the subject from participating in the study.

Diagnostic assessments

18. QTcF $\geq$ 450 msec for males or QTcF $\geq$ 470 msec for females at screening by central overread. If QTcF is above specified limit and there are no other clinically significant abnormalities, repeat assessment is allowed with permission by the Sponsor's Medical Monitor (or designee).
19. Hemoglobin <7.5 g/dL, platelet count <100,000/µL, absolute neutrophils count < 1200/µL at screening.
20. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 times upper limit of normal (ULN) at screening.

21. Total bilirubin > ULN at screening, unless likely related to diagnosis of Gilbert's syndrome, in the opinion of the Investigator.
22. Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 calculated by chronic kidney disease epidemiology collaboration (CKD-EPI).

Prior Clinical Study Experience

23. Treatment with an investigational medication or treatments (eg, hyperbaric oxygen treatment) within the past 30 days or within 5 half-lives of the medication, whichever is longer, prior to screening. (This also includes investigational formulations of marketed products.)
24. Have previously received treatment with GB004/AKB-4924.

Other Exclusions

25. A history or suspected history of alcohol misuse or substance abuse, per the discretion of the principal investigator, within 12 months prior to screening.
26. Female subject who is pregnant or breastfeeding. Female subjects should not be enrolled if they are planning to become pregnant during the time of study participation. A urine pregnancy test is required of all women of child-bearing potential.

5.3. UC Disease Activity Criteria

Subjects meeting the following predefined UC Disease Activity criteria at or after the PCP Week 12 visit and prior to PCP Week 36 visit on IP may enter the OLE and receive GB004 BID treatment. Refer to Table 8 for Mayo score calculation instructions in Appendix 8.

- A Mayo score:
  - with Endoscopic subscore ≥2 using the centrally read endoscopy score from the flexible sigmoidoscopy,

    AND
  - greater than or equal to the Mayo score at the PCP Day 1/Week 0 visit

AND

- Exclusion of other causes of disease activity unrelated to underlying UC (eg, infections), at the discretion of the Investigator

5.4. Screen Failures

Subjects will be assigned a subject number at the time of signing the ICF. Subjects who are not randomized will be labeled as screen failures.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details (including eligibility criteria), and any SAE.

Subjects who are labelled as screen failures may be eligible to rescreen once upon approval by the Sponsor's Medical Monitor (or designee). A new subject number will be assigned if approved to rescreen.

6. INVESTIGATIONAL PRODUCT

6.1. Investigational Product(s) Administered

Each dose of IP will consist of a combination of GB004 tablets and GB004 delayed-release (equivalent term to gastro-resistant) tablets or of matching placebo tablets and will be taken orally BID on a fed stomach at approximately the same time each day, 8 to 12 hours apart.

The GB004 tablets, GB004 delayed-release tablets, and placebo tablets are similar and indistinguishable in terms of appearance, odor, and taste, such that the blind is maintained.

Table 3: Investigational Product Formulation by Treatment Group

Investigational Product Name	**GB004 (Active)** PCP and OLE	**Placebo (Control)** PCP only
Dose Formulation	GB004 round film-coated tablets	Matching placebo round film-coated tablets
Unit Dose Strength	60 mg per tablet	Placebo tablet
Dose regimen	GB004 480 mg BID (PCP and OLE): 4 tablets + 4 delayed-release tablets, BID	Placebo: 8 placebo tablets BID
	GB004 480 mg QD (PCP only): • 4 tablets + 4 delayed-release tablets, QD morning • 8 placebo tablets, QD evening	
Route of Administration	Oral, with food IP to be taken BID (approximately 8 to 12 hours apart) at approximately the same time each day.	
Sourcing	IP will be provided to the site centrally by the Sponsor or designated representative. For exceptions, refer to Appendix 9.	
Packaging	PCP: GB004 tablets, GB004 delayed-release tablets, and GB004 placebo tablets will be packaged in 68 count, 60 cc high-density polyethylene (HDPE) bottles, with child-resistant induction-sealed closures. OLE: GB004 tablets and GB004 delayed-release tablets will be packaged in 68 count, 60 cc high-density polyethylene (HDPE) bottles, with child-resistant induction-sealed closures. Bottles will be dispensed in 4-bottle sets supplying 2 weeks of dosing (sufficient for 17 days of treatment) consisting of 2 bottles used for morning dosing and 2 bottles for evening dosing. Subjects to dose 4 tablets per bottle per day. Refer to the Pharmacy Manual for additional details.	
Labeling	Label text will at a minimum include the protocol number, lot number, storage conditions, and Sponsor name and address. Labels will comply with local regulatory requirements for IPs.	
Storage Requirements	Store at 2°C to 8°C; for more details refer to the Pharmacy Manual.	

6.2. Preparation/Handling/Storage/Accountability

- Bottles containing GB004 tablets or placebo will be shipped to clinical sites using temperature monitoring devices and stored at 2°C to 8°C. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.
- Only randomized subjects may receive IP and only authorized site staff may supply IP. At the study site, all IP must be stored in a secure, refrigerated (2°C to 8°C), environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- Subjects will be provided with coolers for transport of IP from the study site to their home location. Once at home, IP is to be stored in a refrigerator.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Assignment of a Subject Number

At the Screening visit, a unique subject number will be assigned to a subject upon signing of the ICF.

6.3.2. Randomization and Stratification

At PCP Day 1/Week 0 visit, all subjects who meet eligibility criteria will be centrally randomized 1:1:1 to GB004 480 mg BID, GB004 480 mg QD, or placebo using an interactive response technology (IRT) system.

Before the study is initiated, directions for use of the IRT system will be provided to the sites.

Randomization will be stratified by systemic corticosteroid use at baseline (yes/no).

6.3.3. Investigational Product Numbers

IP will be dispensed at the study visits as summarized in the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE). On PCP Day 1/Week 0 visit, the IRT system will assign IP bottle number(s) based on the subject's randomized treatment group.

For subsequent visits when IP is dispensed, the IRT system will assign new IP bottle number(s) based on the subject's randomized/assigned treatment group.

6.3.4. Blinding

Subjects, investigators and site personnel, and the Sponsor (with exceptions described below) will be blinded to individual subject treatment assignments in the PCP. All subjects will dose IP BID to maintain the blind.

The study will be unblinded to the Sponsor at the time of the PCP Week 12 Analysis (see Section 9.4). Therefore, the PCP will be double-blind through PCP Week 12 and will remain blinded to subjects, investigators, and site staff throughout the PCP.

Sponsor (or designee) personnel will have access to unblinded individual subject treatment assignments for the purposes of study-required activities, including management of IP inventory, production of summaries of data for DRC review, and performance of bioanalytical analysis of PK and gene/protein concentrations. These personnel will not be directly involved in the conduct of the study.

A DRC will periodically convene to review unblinded overall safety and emerging efficacy results (refer to Section 9.5.1).

6.3.5. Unblinding of an Individual Subject

The IRT system will be programmed with blind-breaking instructions. In case of a medical emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator, when possible, should make every effort to contact the Sponsor to discuss unblinding a subject's treatment assignment unless this could delay medical emergency treatment of the subject. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

Appropriate personnel at the Sponsor will unblind suspected unexpected serious adverse reactions (SUSARs) for the purpose of regulatory reporting. The Sponsor will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

6.4. Investigational Product Compliance

The first dose of IP will be administered in the clinic on PCP Day 1/Week 0 with food. All subsequent doses will be taken at home with food with the exception of the morning doses at the PCP Week 2, 4, 8, 12, and 36 visits and OLE Enrollment, Week 2, 12 and EOT visits where IP will be administered in the clinic, with food, after pre-dose blood collection as specified in the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE).

After initiation of IP on PCP Day 1/Week 0 visit, subjects will visit the clinic for assessments of IP use as specified in the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE). IP accountability will be assessed by counting returned tablets. Subjects who demonstrate poor IP compliance should be re-educated on the importance of taking their medications as prescribed.

Subjects will be asked to record dosing information on a daily basis in an eDiary.

For additional details refer to Study Reference Manuals.

Guidance for Missed Dose(s)

If a dose is missed, subjects should be instructed to skip the missed dose if there are less than 6 hours before the time of the next dose, resume dosing at their next scheduled dosing time, and document the missed dose.

6.5. Dose Modification

6.5.1. Investigational Product

Dose modification, as described below, may be considered for treatment-related AEs and liver chemistry laboratory abnormalities.

Dose reduction will be prescribed in two steps (as detailed in the Study Reference Manuals):

- First reduction step: IP dose will be reduced by 2 tablets BID
- Second reduction step (only if either treatment-related AE or liver function abnormality persist for 7 days following initiation of first step of dose reduction): IP dose will be reduced further by 1 tablet BID

Treatment-related AEs (other than liver chemistry laboratory abnormalities described below): Dose modification of IP may be undertaken only after consultation and approval from the Sponsor's Medical Monitor (or designee) for AEs assessed by the Investigator as treatment-related, such as tolerability related AEs. Subjects may be requested to attend an unscheduled visit after dose reduction (before potential re-administration of IP at a higher dose as described below), to collect blood samples for safety and PK, if possible.

Liver chemistry laboratory abnormality:

- Dose modification of IP may be undertaken only after consultation and approval from the Sponsor's Medical Monitor (or designee) for confirmed ALT or AST $\geq 3 \times$ ULN and $< 5 \times$ ULN meeting the criterion described in Table 6 in Appendix 7.
- For confirmed ALT or AST $\geq 3 \times$ ULN meeting criteria in Table 7 in Appendix 7, IP should be discontinued.

In both study periods, following dose reduction, IP may be re-administered at a higher dose in consultation with the Sponsor's Medical Monitor (or designee).

After consultation and approval from the Sponsor's Medical Monitor (or designee), subjects with a dose reduction during the PCP may enter the OLE at the reduced dose (reduced number of tablets as specified above) or at full dose (480 mg BID).

6.5.2. Background UC Therapy

New UC therapies may not be started between 2 weeks prior to the screening flexible sigmoidoscopy/colonoscopy and the PCP Week 36 visit. Subjects requiring introduction of new therapies to treat UC will be discontinued from IP as described in Section 7.1.5.

5-ASA

Subjects should remain on their stable UC background oral 5-ASA therapy from 2 weeks prior to screening flexible sigmoidoscopy/colonoscopy used to assess the baseline Mayo score through the duration of their time on study. Any changes in existing UC background therapies should be discussed with the Sponsor's Medical Monitor (or designee), if possible.

Systemic steroid tapering

Subjects receiving oral prednisone ≤ 20 mg/day (or equivalent) or beclomethasone ≤ 5 mg/day or budesonide or budesonide MMX of ≤ 9 mg/day should remain on their stable dose from 2 weeks prior to screening flexible sigmoidoscopy/colonoscopy used to assess the baseline Mayo score through the PCP Week 12 visit. At the discretion of the Investigator, systemic steroids may be tapered after the PCP Week 12 visit as described below. For subjects who cannot tolerate systemic steroid taper without recurrence of clinical symptoms of either UC or steroid withdrawal, the systemic steroid dose may be increased (up to the baseline dose if required).

Prednisone (or equivalent) tapering

- Subjects receiving prednisone at a dose of > 10 mg/day (or equivalent) should have their dose reduced at a rate of 5 mg per week until a 10 mg/day dose is achieved.
- Subjects receiving prednisone at a dose of 10 mg/day (or equivalent) either or when this dose is achieved by tapering during the OLE, are to have their dose reduced at a rate of 2.5 mg per week until discontinuation.

Beclomethasone or Budesonide tapering

- Subjects receiving beclomethasone should taper their dose of 5 mg every day to 5 mg every other day for 2 weeks then discontinue beclomethasone.
- Subjects receiving budesonide or budesonide MMX should taper their dose of 9 mg every day to 9 mg every other day for 2 weeks then discontinue budesonide or budesonide MMX.

6.6. Continued Access to Investigational Product After the End of the Study

No additional intervention is planned beyond the OLE EOT visit.

6.7. Treatment of Overdose

Any dose of IP greater than the prescribed daily dose within the same calendar day will be considered an overdose.

There is no specific treatment recommended to treat an overdose of IP and the subject should receive treatment directed towards any symptoms manifested.

In the event of an overdose, the Investigator should:

- Contact the Sponsor's Medical Monitor (or designee) as soon as possible.

- Closely monitor the subject for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose in the electronic case report form (eCRF).

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Sponsor's Medical Monitor (or designee) based on the clinical evaluation of the subject.

6.8. Concomitant Therapy

At least a 4-hour interval is required between taking IP tablets and mineral supplements, and antacids that contain polyvalent cations (eg, iron, aluminum, and zinc).

Results from in vitro studies indicate that a glucuronide metabolite of GB004, GBD242, may be an inhibitor of OCT2 and CYP2C8.

If sensitive clinical substrates of OCT2 (such as metformin or dalfampridine) are used concomitantly with GB004, refer to the prescribing information of the clinical substrate for assessing the benefit and risk of concomitant use. Initiation of sensitive clinical substrates of OCT2 is permitted only after discussion with the Sponsor’s Medical Monitor (or designee) and consideration of alternatives.

Concomitant use of sensitive substrates of CYP2C8 (eg, repaglinide, rosiglitazone, pioglitazone, and loperamide) is prohibited in this study pending further evaluation of the potential for GBD242 to inhibit CYP2C8 activity clinically.

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Sponsor's Medical Monitor (or designee) should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Prohibited Medications Prior to the Screening Visit and Throughout the Study

Please refer to Appendix 6 for further details regarding prohibited medications.

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND SUBJECT WITHDRAWAL FROM STUDY

7.1. Discontinuation of Investigational Product, Subject Withdrawal from the Study and Stopping Rules

Discontinuation of IP

In some instances, it may be necessary for a subject to permanently discontinue IP.

PCP: Permanent discontinuation of IP does not mean withdrawal from the study, and the subject will be encouraged to remain in the study and continue to complete any remaining PCP study visits as per the SoA (Section 1.3.1 – PCP) if the subject is not enrolling in the OLE. A follow-up visit will be conducted approximately 4 weeks after last dose of IP. The reason for discontinuation of IP will be recorded in the eCRF.

OLE: Subjects who permanently discontinue IP during the OLE will be withdrawn from the study, complete the End of OLE/ET visit, and will be asked to return for a Follow-up visit approximately 4 weeks after their last dose of IP to assess safety.

Withdrawal from the Study

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the institution. The reason for subject withdrawal from the study will be recorded in the eCRF. At the time of withdrawal from the PCP, an Early Withdrawal from Study visit should be conducted, as shown in the SoA (Section 1.3.1 – PCP) and from the OLE, the EOT visit should be conducted as shown in the SoA (Section 1.3.2 – OLE). See the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

A subject may discontinue IP or withdraw from the study for the following reasons:

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by Sponsor
- Study terminated by Sponsor

- Withdrawal by subject

For stopping criteria related to hemoglobin, nausea, and dizziness, refer to Section 7.1.1.

For stopping criteria relating to QTcF prolongation, refer to Section 7.1.2.

For liver chemistry abnormality actions and follow-up assessments, refer to Section 7.1.3 and Appendix 7 and for dose modification, refer to Section 6.5.1.

Pregnancy is a criterion for mandatory permanent discontinuation of IP (see Section 7.1.4).

For stopping criteria related to introduction of new therapy to treat UC between 2 weeks prior to the screening flexible sigmoidoscopy/colonoscopy and the PCP Week 36 visit, refer to Section 7.1.5.

7.1.1. Hemoglobin, Nausea, and Dizziness Stopping Criteria

Individual subjects will be permanently discontinued from IP for any of the following:

- Hemoglobin increase of > 4 g/dL from baseline and above ULN, and is assessed by the Investigator as a related AE.
- Nausea that prevents daily activity, requires outpatient IV hydration, and is assessed by the Investigator as a related AE.
- Dizziness that prevents daily activity, requires medical intervention, and is assessed by the Investigator as a related AE.

7.1.2. QTcF Stopping Criteria

Subjects must permanently discontinue IP for QTcF >500 msec.

7.1.3. Liver Function: Actions and Follow-up Assessments

Liver chemistry will be evaluated as specified in the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE).

For ALT or AST ≥3 × ULN, refer to Appendix 7 for guidelines on monitoring and criteria for possible dose modifications (Section 6.5.1) and temporary interruption of IP with possible restarting criteria and actions.

Any occurrence of a confirmed ALT or AST value ≥3 × ULN will be monitored and evaluated for an etiology (for example viral hepatitis, drug and herbal supplements, environmental exposure, alcohol use, and other) in consultation with the Sponsor (Appendix 2, Table 5).

7.1.4. Pregnancy

A subject must permanently discontinue IP if she becomes pregnant. See Appendix 4 and Section 8.3.5 for additional details.

See the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE) for data to be collected at the time of IP discontinuation (Early Withdrawal from Study visit in PCP and EOT visit for OLE) and follow-up and for any further evaluations that need to be completed.

7.1.5. Introduction of New UC Therapy Stopping Criteria

A subject requiring introduction of a new therapy to treat UC between 2 weeks prior to the screening flexible sigmoidoscopy/colonoscopy and the PCP Week 36 visit must permanently discontinue IP.

7.2. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to engage for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit (for exceptions refer to Appendix 9):

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE). Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the Sponsor's Medical Monitor (or designee) immediately upon occurrence or awareness to determine if the subject should continue or discontinue IP.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- In case of natural disasters or pandemics, some visits/study procedures may be done via virtual visits or at home visits. Refer to Appendix 9 and Study Reference Manuals for more details.

8.1. Efficacy Assessments

8.1.1. Clinical, Endoscopic and Histologic Assessment

Throughout the study, subjects will capture Stool frequency and Rectal bleeding symptoms on a daily basis in an eDiary. For evaluation of eligibility, the Rectal bleeding and Stool frequency subscores of the Mayo score will each be calculated based on the average of the most recent 3 days with non-missing data within 14 days prior to the PCP Day 1/Week 0, excluding the day of and the day after flexible sigmoidoscopy/colonoscopy and the day(s) of bowel preparation, if performed. Subjects bowel preparation for flexible sigmoidoscopy/colonoscopy should follow standard clinical practice. Subjects will be instructed that a stool is defined as a trip to the toilet when the subject has either a bowel movement, or passes blood alone, blood and mucus, or mucus only.

Screening, PCP Week 12, and PCP Week 36 (and at an Unscheduled UC Disease Activity Criteria Assessment visit(s) and the Early Withdrawal from Study visit, if applicable) endoscopic subscores will be assessed by both a central reader (who is blinded to treatment assignment, visit, and subject symptoms) and local endoscopist (who is blinded to treatment assignment). The same local endoscopist assesses the endoscopic subscore for a particular subject throughout the study, if possible. Differences between the local endoscopist and the central reader will be adjudicated by a second blinded central reader as described in the Imaging Charter. Centrally read endoscopic subscores will be used for both eligibility determination and efficacy analyses. Histologic scores (eg, RHI) will be evaluated by a blinded central reader.

Flexible sigmoidoscopy/colonoscopy and histology assessments will consist of assessing the Endoscopic subscore of the sigmoid colon at approximately 15 to 25 cm from the anal verge. Six biopsies will be obtained during the endoscopic procedures from the area that appears to be most affected by UC in this sigmoid colon segment.

Biopsies may also be evaluated for PK, gene expression, and immunohistochemistry signals of biological activity.

8.1.2. Mayo Score and Modified Mayo Score

Mayo score is used for inclusion into the study rather than a Modified Mayo score (used to evaluate efficacy) given the limited information available at the study inception regarding Modified Mayo score cut points that define a mild-to-moderate patient population.

The Mayo score is a conventional assessment of UC disease activity and is commonly used in clinical studies of UC. The score is composed of four subscores, each ranging from 0 to 3, that are summed to give a total score ranging from 0 to 12 points, with higher scores indicating greater severity (Adapted from Schroeder, 1987):

1. Stool frequency:

   0 = Normal number of stools for this subject

   1 = 1 to 2 stools more than normal

   2 = 3 to 4 stools more than normal

   3 = 5 or more stools than normal

Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency. The control value is the number of stools in a 24-hour period when the subject was in remission from UC, or, if the subject does not report having previously achieved remission from UC, the number of stools the subject reports per day before initial onset of signs and symptoms of UC.

2. Rectal bleeding:

   0 = No blood seen

   1 = Streaks of blood with stool less than half the time

   2 = Obvious blood with stool most of the time

   3 = Blood alone passes

   The daily bleeding score represents the most severe bleeding of the day.

3. Findings on endoscopy:

   0 = Normal or inactive disease

   1 = Mild disease (erythema, decreased vascular pattern)

   2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)

   3 = Severe disease (spontaneous bleeding, ulceration)

4. Physician's Global Assessment

   0 = Normal

   1 = Mild disease

   2 = Moderate disease

   3 = Severe disease

   The PGA acknowledges the three other criteria, the subject's recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the subject's performance status. It is recommended that the same physician performs the PGA for a particular subject throughout the study.

The Modified Mayo score is an endpoint measure composed of: Stool frequency, Rectal bleeding, and Endoscopic subscores (where the Endoscopic subscore value of 1 does not include friability), each ranging from 0 to 3, that are summed to give a total score ranging from 0 to 9 points, with higher scores indicating greater severity.

The Partial Mayo score is an endpoint measure composed of: Stool frequency, Rectal bleeding, and PGA subscores, each ranging from 0 to 3, that are summed to give a total score ranging from 0 to 9 points, with higher scores indicating greater severity.

The 6-point Mayo score is an endpoint measure composed of: Stool frequency and Rectal bleeding subscores, each ranging from 0 to 3, that are summed to give a total score ranging from 0 to 6 points, with higher scores indicating greater severity.

8.1.3. Robarts Histopathology Index (RHI) Score, Geboes Score and Ulcerative Colitis Index-100

The RHI is a validated instrument that measures histological disease activity in UC. The RHI consists of 4 items: chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in epithelium, and erosion or ulceration. The RHI score ranges from 0-33 and is derived from Geboes score (Mosli, 2017).

RHI = 1 x chronic inflammatory infiltrate level (4 levels)
+ 2 x lamina propria neutrophils (4 levels)
+ 3 x neutrophils in epithelium (4 levels)
+ 5 x erosion or ulceration (4 levels after combining Geboes 5.1 and 5.2)

The Geboes score is divided into 6 grades: architectural changes [grade 0], chronic inflammatory infiltrate [grade 1], lamina propria eosinophils and neutrophils [grade 2A and 2B], neutrophils in epithelium [grade 3], crypt destruction [grade 4] and erosions or ulcerations [grade 5]. The Geboes score is calculated as the highest grade with a corresponding subgrade score > 0, excluding Geboes Grade 2A, and ranges from 0 to 5.

The Ulcerative Colitis Index-100 (UC-100) score is the composite index (1 + 16 x Stool frequency subscore [0 to 3] + 6 x Endoscopic subscore [0 to 3] + 1 x RHI score [0 to 33]) (Jairath, 2019).

8.2. Safety Assessments

8.2.1. Physical Examinations

A complete physical examination will be performed at timepoints designated in the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE) and will include:

- General appearance/inspection
- Skin
- Neck
- Lymphatic
- Respiratory
- Cardiovascular
- Abdominal system
- HEENT (head, eyes, ears, nose, throat)
- Other- for those body systems, not listed above considered necessary per PI's discretion

A symptom-directed physical examination will be conducted if clinically indicated throughout the study. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Heart rate, respiratory rate, temperature and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with the subject in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available or if the automated cuff sizes available are not large enough for the subject's arm circumference.
- Vital signs will be measured after 5 minutes rest and prior to ECG measurements on days where the 12-lead ECG will be obtained.
- Height and weight will also be measured and recorded. Height will only be recorded at Screening.

8.2.3. Electrocardiograms

- 12-lead ECGs will be obtained at timepoints specified in the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- Subjects with evidence of a significant abnormality in the 12-lead ECGs obtained at screening, including prolongation of the QTc interval, will not be eligible to randomize into the study.
- ECG will be centrally read by the Sponsor's designee via the electronic portal.
- Original paper tracings and tracing copies of the ECGs should be stored in the source documents.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE) for the timing and frequency. Details for collection, processing, and shipping of samples to the central laboratory are provided in a separate Central Laboratory Manual.
- The Investigator must review and document review of the laboratory report. The Investigator must record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significant during participation in the study should be repeated as medically indicated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor's Medical Monitor (or designee).
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Central Laboratory Manual and the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE).

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and SAE can be found in Appendix 3.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator and qualified designees remain responsible for following AEs that are serious, considered related to the IP or study procedures, or that caused the subject to discontinue from IP or from the study (see Section 7.1).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected beginning at the time of consent through the end of the follow-up period (including PCP and OLE). All medical occurrences, with the exception of SAEs, that begin after obtaining ICF and before first dose of IP will be recorded on the Medical History section of the eCRF and not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately upon the site learning of an event and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of an IP under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- Investigator Safety Reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy, and then the reports will be forwarded to Investigators as necessary.
- An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study IP and until birth.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Worsening of UC will be evaluated by efficacy assessments (Section 8.1) and is a disease-related outcome not qualifying as an AE unless the Investigator considers the worsening UC to have met the definition of an SAE (Appendix 3). Worsening UC meeting the definition of an SAE will be reported in the appropriate eCRF. Worsening UC not meeting the definition of an SAE should not be reported as an AE. Worsening UC will be evaluated by efficacy endpoints and by the occurrence of SAEs, and will be monitored by the Sponsor on a routine basis.

8.4. Pharmacokinetics

Blood will be collected and used for the measurement of plasma concentrations of GB004, and metabolites of GB004 (glucuronide [GBD242] and glucoside [GBD243]) as specified in the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE). On the visit day, the subject should be instructed to take the dose at the site following the predose blood sample draw. If a subject withdraws early from the study, a blood sample may also be taken, if possible.

Colon tissue samples will be collected during flexible sigmoidoscopy/colonoscopy and may be used for measuring concentration of GB004.

Additionally, stool samples may be analyzed for levels of GB004.

Samples may also be used for assay development and characterization of potential metabolites of GB004.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

8.5. Pharmacodynamics and Biomarkers

Blood, stool, and colonic biopsy samples should be collected as designated in the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE) and may be used for exploratory assessment of TE/PD biomarkers, eg, histology, c-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, gene expression, and immunohistochemistry, e.g. HIF-1α, EGLN1-2-3, etc.

Samples may be stored at a facility selected by the Sponsor, to enable further analysis of biomarker responses to GB004, for a maximum of 8 years (or according to local regulations) following the last subject's last visit for the study.

Residual blood, and urine samples may be stored for potential future identification of factors or profiles that correlate with measures of response to GB004.

Please refer to the study specific Central Laboratory Manual for PD biomarker details.

8.6. Pharmacogenetic

Pharmacogenetic (PGx) analyses may be performed on any bio-sample from subjects who have consented for PGx sampling. Subject confidentiality will be maintained.

Suitable bio-samples should be collected from all subjects, where permitted by law and local authorities. Those subjects who are prohibited from participating in the PGx research by law and/or local authorities, and those subjects providing a written (documented) opt-out, may still participate in the study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Placebo-Controlled Period

The PCP is designed to demonstrate the superiority of each GB004 treatment group to placebo on the primary endpoint of the proportion of subjects with clinical remission at PCP Week 12. The PCP is also designed to demonstrate the superiority of each GB004 treatment group to placebo on the primary endpoint of the proportion of subjects with clinical remission at PCP Week 36.

9.1.2. OLE

The purpose of the OLE period is to evaluate the long-term safety and tolerability of GB004. No formal statistical hypotheses are being tested.

9.2. Sample Size Determination

9.2.1. Placebo-Controlled Period

A total sample size of approximately 195 subjects (approximately 65 per treatment group, randomized 1:1:1, with stratification by systemic corticosteroid use at baseline [yes/no]) is estimated to provide approximately 80% power to detect a difference of 20.4% between each GB004 treatment group and placebo for the primary endpoint of proportion of subjects with clinical remission at PCP Week 12 based on a chi-squared test at an 0.050 two-sided level of significance. This assumes the proportion of subjects with clinical remission at PCP Week 12 is 10% in the placebo group and 30.4% in each GB004 treatment group and a dropout rate by PCP Week 12 of approximately 8%. Subjects with missing clinical remission status at PCP Week 12 will be considered as having not met the primary endpoint.

Using the same sample size assumptions as above for the primary endpoint of proportion of subjects with clinical remission at PCP Week 12 (ie, a difference of 20.4% between each GB004 treatment group and placebo, with a 10% proportion in the placebo group), there will be approximately 80% power for the secondary endpoint of the proportion of subjects with clinical remission at PCP Week 36 based on a chi-squared test at an 0.050 two-sided level of significance. Subjects with missing clinical remission status at PCP Week 36 will be considered as having not met the endpoint.

9.2.2. OLE

There is no formal sample size calculation for this period of the study. This is an extension of the PCP. Subjects must complete at least 12 weeks of treatment in the PCP prior to dosing in the OLE. Therefore, the maximum number of subjects potentially eligible to participate in the OLE will not be greater than the total number of subjects randomized in the PCP (approximately 195 subjects).

9.3. Populations for Analyses

9.3.1. Placebo-Controlled Period

The following major analysis populations are defined for the PCP:

- Intent-to-treat (ITT) Population: All subjects who are randomized and receive at least 1 dose of IP, with subjects grouped according to randomized treatment.
- Safety Population: All subjects who receive at least 1 dose of IP, with subjects grouped according to their actual treatment.

9.3.2. OLE

The following major analysis populations are defined for the OLE:

- OLE Safety Population: All subjects who receive at least one dose of IP in the OLE.
- GB004-treated Safety Population: All subjects who receive at least one dose of GB004 in PCP and/or OLE.

9.4. Statistical Analyses

Three separate formal statistical analyses will be performed:

- The PCP Week 12 Analysis will be conducted after all subjects either complete the PCP Week 12 visit or withdraw from the study prior to completion of the PCP Week 12 visit. This analysis will evaluate endpoints at or up through PCP Week 12.
- The PCP Final Analysis will be conducted after all subjects either complete the PCP or withdraw from the study prior to completion of the PCP; This analysis will evaluate all PCP endpoints.
- The OLE Final Analysis will be conducted after all subjects either complete the OLE period or withdraw from the study prior to completion of the OLE period.

The study will be unblinded to the Sponsor at the time of the PCP Week 12 Analysis. Therefore, the PCP will be double-blind through PCP Week 12 and will remain blinded to subjects, investigators, and site staff throughout the PCP.

In general, continuous variables will be summarized using the number of subjects with non-missing data, mean, standard deviation, standard error (where appropriate), median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

For the PCP Week 12 Analysis and the PCP Week 36 Analysis, baseline will be defined as the last non-missing value prior to first dose of IP in the PCP. For the OLE Analysis, GB004 baseline will be defined as the last non-missing value prior to the first dose of GB004 in the study.

This section is a summary of the planned statistical analyses of the primary, secondary, and safety endpoints.

9.4.1. PCP Week 12 Analysis

9.4.1.1. Efficacy Analyses

The ITT population will be utilized for efficacy analyses.

Primary Endpoint

The primary endpoint of the proportion of subjects with clinical remission at PCP Week 12 will be compared between each GB004 treatment group and placebo by a Cochran-Mantel Haenszel (CMH) chi-squared test (Mantel, 1959) stratified by systemic corticosteroid use at baseline (yes/no) with a two-sided 0.050 level of significance. If stratum cell sizes are too small based on the Mantel-Fleiss criterion (Mantel, 1980), Pearson's chi-squared test will be used instead.

For the comparison of each GB004 treatment group versus placebo, the p-value from the CMH chi-squared test will be reported, along with the estimated Mantel-Haenszel common odds ratio across strata and corresponding 95% CI. The number and proportion of subjects meeting the primary endpoint and corresponding 95% Wilson (Score) CIs (Wilson, 1927) will be summarized by treatment group. The absolute difference in proportion between each GB004 treatment group and placebo will also be summarized, with the 95% CI for the absolute difference based on the Newcombe continuity-corrected method (Newcombe, 1998).

In the primary analysis of the primary endpoint, subjects with missing clinical remission status at PCP Week 12 will be considered as having not met the primary endpoint. The primary endpoint will also be analyzed using various other methodological approaches for handling subjects with missing data as sensitivity analyses.

Secondary Endpoints

The secondary endpoints of the proportion of subjects with clinical response at PCP Week 12, the proportion of subjects with histologic remission at PCP Week 12, the proportion of subjects with endoscopic improvement at PCP Week 12, and the proportion of subjects with mucosal healing at PCP Week 12 will be analyzed using the same approach as the primary endpoint. Histologic remission at PCP Week 12 and mucosal healing at PCP Week 12 will be evaluated among subjects with Baseline lamina propria neutrophils and neutrophils in epithelium RHI subscores > 0.

These secondary endpoints will be assessed at a two-sided level of significance of 0.050 for the comparison of each GB004 treatment group and placebo.

9.4.1.2. Safety Analyses

All safety analyses will be performed using the Safety Population. Safety data will be listed by subject.

Safety analyses will be focused on treatment-emergent AEs, defined as an AE with onset on or after the start of study treatment. The incidence of AEs will be summarized by treatment group, including the incidence by system organ class and preferred term, severity, and relationship to study drug, the incidence of SAEs, the incidence of AEs that lead to discontinuation of study drug, and the incidence of AEs that lead to withdrawal from study.

9.4.2. PCP Final Analysis

The PCP Final Analysis will be performed using the same methodological approaches as the PCP Week 12 Analysis.

9.4.3. OLE Final Analysis

The OLE Safety population will be used as the primary analysis population for safety analyses, which will be based on data from the OLE period.

Select safety analyses will summarize the safety experience of all subjects treated with GB004 in the PCP or the OLE period, using the GB004-Treated Safety population, with data combined across the PCP and OLE.

Additionally, in order to inform assessment of whether there appear to be any new or worsening safety signals in the OLE period, select safety analyses will summarize the placebo-controlled safety experience in the PCP side-by-side with the continuing GB004 safety experience in the OLE period (using subjects in the OLE Safety population who were previously treated with GB004).

Safety analyses will be focused on TEAEs, defined as an AE with onset on or after the start of study treatment in the respective analysis. The incidence of AEs will be summarized by treatment

group, including the incidence by system organ class and preferred term, severity, and relationship to study drug, the incidence of SAEs, the incidence of AEs that lead to discontinuation of study drug, and the incidence of AEs that lead to withdrawal from study. The incidence of AEs and SAEs by system organ class and preferred term may also be presented by time intervals. Incidence rates of AEs adjusted for time on study (eg, number of subjects per 1000 subject-years) may also be presented.

9.5. Interim Analyses

During the OLE, interim analyses will be performed as needed for regulatory reporting, safety updates, publications, or as otherwise required by the Sponsor.

9.5.1. Data Review Committee

A DRC, comprised of Sponsor representatives not directly involved in the conduct of the study, and external expert physician(s), will regularly monitor overall safety and emerging efficacy results on an unblinded basis, as well as general aspects of study conduct, to ensure that the benefits and risks of study participation remain acceptable.

Based on these regular reviews of emerging results, the DRC will recommend continuation, modification, or termination of the study.

Composition of the DRC, meeting structure, schedule, and procedures, the content and format of DRC reports, and other relevant details will be determined in consultation with DRC members and detailed in a separate DRC charter.

10. APPENDICES

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

A clinical study report will be developed by the Sponsor at completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

Data Quality Assurance

- All subject data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator per ICH-GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further IP development

Publication Policy

The publication policy for this study is located within the Clinical Study Agreement with the Investigator and/or Institution.

APPENDIX 2. CLINICAL LABORATORY TESTS

- The tests detailed in Table 4 will be performed by the central laboratory (for exceptions see Appendix 9).
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 4: Protocol-Required Safety Laboratory Assessments

Hematology	
White blood cell count (WBC) with differential (% and absolute) for Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils Hemoglobin Platelet count	Red blood cell (RBC) with indices (mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]) Hematocrit
Clinical Chemistries	
Alanine Aminotransferase (ALT) Alkaline phosphatase Total and direct bilirubin (fractionated) Albumin Calcium Sodium Glucose Chloride	Aspartate Aminotransferase (AST) Gamma-glutamyl transferase (GGT) Blood urea nitrogen (BUN) Lactate dehydrogenase (LDH) Creatinine Potassium Total protein Bicarbonate C-reactive protein (CRP)
Urinalysis	
Basic Urinalysis (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen)	
Other Laboratory Assessments	
• Serology (hepatitis B surface antigen [HBsAg], hepatitis C virus antibody, human immunodeficiency virus [HIV] antibody). If positive HBsAg positive, confirmatory hepatitis B virus DNA will be tested. If hepatitis C virus antibody is positive, hepatitis C virus RNA will be tested. • Estimated Glomerular Filtration Rate (eGFR) calculated by chronic kidney disease epidemiology collaboration (CKD-EPI) • Serum markers: Iron, Transferrin, Total iron binding capacity, Hepcidin, Ferritin, Zinc • Plasma markers: EPO, vascular endothelial growth factor (VEGF) • Coagulation panel: International normalized ratio (INR) • Serum Pregnancy Test	

- Urine Pregnancy Test

The additional tests listed in Table 5 will be collected only as part of liver safety actions and follow-up (see Section 7.1.3).

Table 5: Liver Safety Laboratory Assessments

- Hepatitis A immunoglobulin M (IgM) antibody
- HBsAg
- Hepatitis C virus antibody
- Hepatitis E IgM antibody
- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing)
- Anti-nuclear antibody
- Anti-smooth muscle antibody
- Type 1 anti-liver kidney microsomal antibodies
- Quantitative total immunoglobulin G (IgG) or gamma globulins
- Serum acetaminophen assay
- Serum creatine phosphokinase (CPK)
- Lactate dehydrogenase (LDH)
- Complete Blood Count with differential
- Obtain blood sample for pharmacokinetic (PK) analysis

The above assessments will be conducted only if required.

APPENDIX 3. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
• An adverse event, AE, is any untoward medical occurrence in a subject or clinical study subject whether or not considered related to the IP. • **NOTE**: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IP.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after IP administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as SAE if they fulfil the definition of an SAE.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Fluctuations in UC disease activity that do not worsen compared to a subject's medical history of UC

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between IP and each occurrence of each AE/SAE.
- **Related** – The AE is known to occur with the IP, there is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the IP caused the event, there is no temporal relationship between the IP and event onset, or an alternate etiology has been established.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always assess causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The mechanism for reporting an SAE to the Sponsor will be the electronic data capture system.
- If the electronic system is unavailable, then the site will contact the Sponsor's Medical Monitor (or designee) in order to report the event and submit the paper SAE report form via the contacts below within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information via contact to the Sponsor's Medical Monitor (or designee) and submitting the paper SAE report form via the contacts below.
- Contacts for SAE reporting can be found in Study Manual.

APPENDIX 4. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

1. Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IP, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Female subjects on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before baseline into the study.

2. Contraception Guidance

Male Participants:

Male subjects are eligible to participate if they agree to the following from consent through at least 90 days after the last dose of IP:

- Refrain from donating sperm

  PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier (condom)

Female Participants:

A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in the table below, from 30 days prior to screening, during the study period, and for 30 days after the last dose of IP and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of IP.

- A WOCBP must have a negative highly sensitive pregnancy test within 24 hours before the first dose of IP. If the urine test is positive or cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.

Highly Effective Methods[a] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[b]
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[a] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
a. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
b. Acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

3. Collection of Pregnancy Information

Male subjects with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Follow-up must be conducted at least until birth or termination of the pregnancy.

Female subjects who become pregnant

The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy.

The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Follow-up must be conducted at least until birth or termination of the pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the IP by the Investigator will be reported to the Sponsor as described in Appendix 3. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will discontinue IP or be withdrawn from the study.

APPENDIX 5. PHARMACOGENETICS

Use and Analysis of DNA

- Germ line variation may impact a subject's response to IP, susceptibility to, and severity and progression of disease. Variable response to IP may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a biosample may be collected for analysis from subjects.
- Samples may be analyzed for genetic variations in genes which dramatically affect the pharmacokinetics of GB004, the safety, and/or efficacy profile. Often times, a large variability in the plasma concentration–time profiles of any medicine can be linked to loss of function mutations in the drug metabolizing enzymes and/or transporters. For example, substantial efforts have been made in reducing the risk of drug–drug interactions related to cytochrome P450 enzymes and variability caused by polymorphic expression of metabolizing enzymes (eg, UGT1A1, UGT1A6, UGT2B7). The effects of single nucleotide polymorphisms (SNPs) on the PK of GB004 uncovered in the course of this study may help guide future clinical studies and regulatory review of GB004. Additional pharmacogenetic analyses may be conducted if it is hypothesized that doing so may help resolve issues with the clinical data (eg, safety and/or pharmacodynamic observations) during the study.
- The results of these analyses may be reported in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GB004 continues but no longer than 8 years or other period as per local requirements.
- The Sponsor may elect to measure the naturally occurring variation across a range of relevant pharmacogenetic markers using modern laboratory assays, eg, the ThermoFisher DMET™ Plus Solution. This assay, for example, would cover 1,936 genetic variants across 231 relevant genes, using a single array, and would include many genetic variants that cannot easily be detected using other assays, eg, SNPs and indels with secondary polymorphisms in close proximity, triallelic markers, and variants from multi-gene families. Particular emphasis would, in this case, be placed on covering the PharmaADME "Core ADME Genes" (32 genes) and PharmaADME "Core Markers" (185 variants). If the Sponsor finds it necessary, it may move beyond the PharmaADME core content to cover common and functional variants associated with the mechanism of action of GB004, hepatic detoxification pathways, and/or other markers associated with adverse drug events eg, CYP3A4 (392A>G), structural variants in transporter genes – an important pharmaceutical target eg, ABCG2 (421C>A), enrichment for mutations in absorption, distribution, metabolism, elimination (ADME) regulatory genes eg, PPARD, inclusion of many population specific markers eg, VKORC1.

APPENDIX 6. PROHIBITED MEDICATIONS

The following medications are prohibited throughout the study:

- Azathioprine
- 6-mercaptopurine
- Any per rectum therapy (eg, enemas or suppository formulations of steroids or 5-aminosalicylates) except those required for flexible sigmoidoscopy preparation
- Marketed biologic therapies for any condition such as adalimumab, infliximab, vedolizumab, rituximab, golimumab, ustekinumab
- Tofacitinib, oral cyclosporine, sirolimus, mycophenolate mofetil
- Epoetin alfa
- Cholestyramine or other drugs interfering with enterohepatic circulation
- Any investigational agent other than GB004
- Chronic NSAID use (occasional use of NSAID, acetaminophen, or aspirin up to 325 mg/day is allowed)
- Anti-diarrheal medications (eg, loperamide, diphenoxylate/atropine)
- Strong CYP3A inhibitors and/or CYP3A inducers (eg, boceprevir, cobicistat, conivaptan, danoprevir, ritonavir, elvitegravir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, ombitasvir, dasabuvir, posaconazole, saquinavir, telaprevir, tipranavir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort)
- Inhibitors of UGT (eg, atazanavir; oral cannabidiol [≥5 mg/kg/day]; elbasvir and grazoprevir; encorafenib; epirubicin; oral fluconazole; fostamatinib; glecaprevir and pibrentasvir; isavuconazole; nelfinavir; ombitasvir and paritaprevir and ritonavir and dasabuvir; pazopanib; regorafenib; valproic acid).
- Dofetilide
- Sensitive CYP2C8 substrates (eg, repaglinide, rosiglitazone, pioglitazone, loperamide).

APPENDIX 7. LIVER SAFETY – ACTIONS AND FOLLOW-UP ASSESSMENTS

Liver assessments performed as part of the standard clinical chemistry evaluations will be evaluated as specified in the SoA (Section 1.3.1 – PCP and Section 1.3.2 – OLE) and Appendix 2 (Table 5). Parameters will include ALT, AST, GGT, ALP, total bilirubin, and direct bilirubin.

For subjects with ALT or AST ≥ 2 × ULN and < 3 × ULN, confirm the value within 72 hours. Contact the Sponsor's Medical Monitor (or designee) to determine if additional liver monitoring is indicated. Blood sample for pharmacokinetic (PK) analysis should also be obtained.

For liver chemistry abnormalities actions and follow-up assessments refer to Section 7.1.3, and for dose modification refer to Section 6.5.1. The criteria requiring additional liver monitoring with possible IP interruption is provided in Table 6.

Table 6: Liver Chemistry Criteria Requiring Additional Monitoring with Possible Dose Modification of Investigational Product

Criteria	Actions
ALT or AST ≥ 3× ULN and < 5× ULN AND **bilirubin ≤ 2× ULN** AND **without symptoms believed to be related to liver injury or hypersensitivity**[a] AND **who can be monitored weekly for 4 weeks**	• Notify the Sponsor's Medical Monitor (or designee) within 24 hours of learning of the abnormality to discuss subject safety. "Liver Safety Laboratory Assessment" in Table 5 may be requested by the Sponsor's Medical Monitor (or designee). • Confirm values within 24-48 hours via repeat laboratories (include ALT, AST, GGT, ALP, total bilirubin, direct bilirubin, and INR). • If unable to obtain repeat laboratories within 24-48 hours, decision to continue or interrupt IP will be determined by the Investigator in consultation with the Sponsor's Medical Monitor (or designee). • If repeat laboratories confirm that criteria are met, the dose of IP may be reduced, with approval from the Sponsor's Medical Monitor (or designee), to doses mentioned in Section 6.5.1. • Subject must return weekly or more frequently for repeat liver chemistry tests (ALT, AST, GGT, ALP, total bilirubin, direct bilirubin, and INR) until the abnormalities resolve, stabilize or return to baseline. • If at any time the subject meets liver chemistry interruption criteria (as specified in Table 7), then follow the instructions in "Liver Chemistry – Investigational Product Interruption Criteria" in Table 7 and in consultation with the Sponsor's Medical Monitor (or designee) initiate relevant assessment procedures.

[a] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

Table 7: Liver Chemistry Criteria Requiring Investigational Product Interruption and Additional Monitoring

Liver Chemistry – IP Interruption Criteria	
ALT/AST (single occurrence)	ALT or AST ≥ 5× ULN
ALT/AST	ALT or AST ≥ 3× ULN persists for ≥ 4 weeks
+ Bilirubin [a,b]	ALT or AST ≥ 3× ULN and bilirubin > 2× ULN (> 35% direct bilirubin)
+ INR [b]	ALT or AST ≥ 3× ULN and international normalized ratio (INR) > 1.5, if INR measured
+ Cannot Monitor	ALT or AST ≥ 3× ULN and cannot be monitored weekly for 4 weeks
+ Symptomatic [c]	ALT or AST ≥ 3×ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
ACTIONS	
• **Immediately** interrupt IP. • Report the event to the Sponsor's Medical Monitor (or designee) **within 24 hours.** • Repeat liver chemistry tests (include ALT, AST, GGT, ALP, total bilirubin, direct bilirubin, and INR) and perform the Liver Safety Laboratory Assessments (Table 5) within **24 hours.** • If the repeat liver chemistry test confirms the criteria are met, monitor the subject until liver chemistry test abnormalities resolve, stabilize, or return to baseline after discussion with the Sponsor's Medical Monitor (or designee) (see **MONITORING**). • **Do not restart** IP unless Sponsor's Medical Monitor (or designee) approval is granted. If restart is granted, IP may be restarted at modified dose (Section 6.5.1). • If restart **not granted**, permanently discontinue IP and continue subject in the study for any protocol specified follow up assessments. • Complete an SAE data collection tool if the event also met the criteria for an SAE.[b] • Liver imaging (ultrasound, magnetic resonance, or computerized tomography), liver biopsy, and/or specialist consultation to evaluate liver disease may be requested by the Sponsor.	
MONITORING	
If ALT or AST ≥ 3× ULN AND bilirubin > 2× ULN or INR > 1.5: • Monitor subject twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline.	**If ALT or AST ≥ 3× ULN AND bilirubin ≤ 2× ULN and INR ≤ 1.5:** • Monitor subjects weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue IP if ALT or AST ≥ 3 × ULN **and** bilirubin > 2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT or AST ≥ 3 × ULN **and** bilirubin > 2 × ULN (> 35% direct bilirubin) or ALT or AST ≥ 3 × ULN **and** INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to subjects receiving anticoagulants. INR is not part of routine laboratory assessments in this study.

[c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia)

APPENDIX 8. INSTRUCTIONS FOR CALCULATING MAYO SCORE FOR UC DISEASE ACTIVITY CRITERIA ASSESSMENT

Table 8 provides instructions for calculating the Mayo score for assessing the predefined UC disease activity criteria at or after the PCP Week 12 visit and prior to the PCP Week 36 visit (Section 5.3) while the subject is receiving IP.

Table 8: Instructions for Calculating Mayo Score For UC Disease Activity Criteria Assessments (at or after PCP Week 12 visit and prior to PCP Week 36 visit)

Timepoint	Instructions
At PCP Week 12 visit (post endoscopy)	• Use PCP Week 12 visit Mayo score and centrally read Endoscopic subscore
At PCP post-Week 12 visit and prior to PCP Week 36 visit	• Use – Updated centrally read Endoscopic subscore (unscheduled) if previous flexible sigmoidoscopy was conducted > 4 weeks prior, otherwise use PCP Week 12 centrally read Endoscopic subscore – Updated Stool frequency subscore, Rectal bleeding subscore, and PGA

Notes:

- If, after the PCP Week 12 visit and prior to the PCP Week 36 visit, the investigator becomes aware of an increase in UC disease activity outside the normal visit schedule in a subject on IP, then a subject may also be evaluated at an Unscheduled UC Disease Activity Criteria Assessment visit as specified in the SoA (Section 1.3.1).
- Endoscopic subscores will be assessed by both a central reader (who is blinded to treatment assignment, visit, and subject symptoms) and local endoscopist (who is blinded to treatment assignment). Differences between the local endoscopist and the central reader will be adjudicated by a second blinded central reader as described in the Imaging Charter.

APPENDIX 9. GUIDANCE TO ADDRESS A PANDEMIC OR OTHER GLOBAL HEALTH EMERGENCIES AND POTENTIAL IMPACT ON THE CLINICAL STUDY

In the occurrence of a global health emergency affecting the conduct of the ongoing study, such as the COVID-19 pandemic, study conduct may be adjusted due to subjects being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks.

Adjustments to the GB004-2101 protocol may be made as described below, in line with global regulatory authorities guidance in order to ensure the safety of study participants, maintain compliance with GCP, and minimize the risks to study integrity during the COVID-19 pandemic (EMA, April 2020; FDA, March 2020; Health Canada, 03 April 2020; MHRH, 22 April 2020). Member states within the National Competent Authorities may issue their own guidance requiring country specific recommendations to be followed.

Informed Consent

- If written consent by the study subject is not possible (for example because of physical isolation due to COVID-19 or other global health emergencies), consent could be given orally by the study subject.
- Study subjects and the person obtaining consent could sign and date separate ICFs.
- In case a written informed consent cannot be obtained at the clinical site, electronic informed consent can be obtained remotely. Alternatively, the consent form may be sent to the subject or the subject's legally authorized representative by facsimile or e-mail, and the consent interview may then be conducted by telephone/teleconference when the subject or subject's legally authorized representative can read the consent form during the discussion; the subject or subject's legally authorized representative will be requested to sign and date a blank piece of paper with a written statement affirming that they agree to participate in the study.
- If re-consent is necessary for the implementation of **new urgent changes in study conduct** (mainly expected for reasons related to global health emergencies or important safety issues for other studies), alternative ways of obtaining may include contacting the study subject via phone or video-calls and obtaining oral consents, to be documented in the study subjects' medical records, supplemented with e-mail confirmation.
- The informed consent procedure is to remain compliant with the study protocol as well as local regulatory requirements. All relevant records should be archived in the investigator's site master file. A correctly signed and dated informed consent form should be obtained from the study subjects later, as soon as possible.

Study Visits and Procedures

- COVID-19 screening procedures that may be mandated by the health care system in which a clinical study is being conducted do not need to be reported as an amendment to the protocol even if done during clinical study visits. The Investigator in

consultation with the Sponsor will decide if it is in the best interest of COVID-positive subjects to remain in the study.

- In the case of missed visits due to global health emergencies (or other health pandemic) related reasons:
  - The site should make every effort to contact the study subject to confirm and document the reason for the missed visit, and at minimum evaluate AEs/SAEs, and concomitant medications in order to assess subject safety.
  - The study subject should continue to collect the daily diary responses on the eDiary.
- In order to maintain the integrity of the study, alternative methods of collecting study procedures may be considered where possible:
  - In cases where global health emergencies-related circumstances preclude a visit to the investigative site, remote visits (eg, by telemedicine or phone contact) will be allowed for relevant study procedures.
  - In certain situations, with Sponsor approval, and according to site business continuity plans, home visits may be used to collect laboratory samples and assessments as required by the protocol.
  - In certain situations, with Sponsor approval, a local laboratory may be used to collect laboratory samples as required by the protocol. Local analysis can be used for safety decisions. In addition, local laboratory can be used for study endpoints if samples drawn at the local laboratory cannot be shipped to the central laboratory.
  - Study assessments will only be conducted in a remote manner if they can be done without affecting the wellbeing of the subject during the study and with the same level of scientific integrity as assessments conducted in a physical study center.
  - Remote study assessments can be completed via online technology. The subject may interact with study personnel using online communication tools which incorporate telemedicine.
  - Serum pregnancy tests can be performed if urine pregnancy cannot be performed.
  - For flexible sigmoidoscopy assessments in the PCP at the PCP Week 12 visit, PCP Week 36 visit, Unscheduled UC Disease Activity Criteria Assessment visit(s) and Early Withdrawal from Study visit, other options such as mobile endoscopy may be considered with Sponsor's approval.
  - If a subject is unable to complete the PCP Week 12 and/or Week 36 flexible sigmoidoscopy within the required timeframe (per SoA), there is flexibility to conduct the endoscopy up to 14 days beyond the visit window for the planned Week 12 and/or Week 36 timepoint while continuing on IP (if the subjects has not previously permanently discontinued IP); in this case, an unscheduled visit will be conducted at the planned Week 12 and/or Week 36 timepoint remotely (eg, by telemedicine) to collect AEs and concomitant medication (additional IP will be

dispensed as needed); the Week 12 and/or Week 36 visit assessments will be required at the clinic within 3 days post-endoscopy.

Supply of Investigational Product

- Alternative methods of supplying IP to enrolled study subjects (eg, direct-to-patient shipment from site) may be considered where possible.
- Additional IP will not be released to the subject without an evaluation of subject safety, including protocol-required laboratory results (at a minimum hematology, clinical chemistries and pregnancy for WOCBP), and clearance communicated to the subject. Subjects must also consent for IP shipment.

Monitoring and Audits

- Certain Sponsor oversight responsibilities, such as monitoring and quality assurance activities need to be re-assessed and temporarily, alternative proportionate mechanisms of oversight may be required. On-site audits will be avoided or postponed, and if permitted under local regulations, social distancing restrictions should apply.
- Cancelling or postponing of on-site monitoring visits and extending of the period between monitoring visits will be allowed.
- To the extent on-site monitoring remains feasible, it should take into account national, local and/or organizational social distancing restrictions.
- Centralized monitoring can be considered for data acquired by electronic data capture systems (eg, eCRFs, central laboratory or ECG / imaging data, electronic patient reported outcomes, etc.) that are in place or could be put in place provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner.
- Off-site monitoring can be conducted and will include phone calls, video visits, e-mails or other online tools in order to discuss the study with the investigator and site staff. Remote monitoring should be focused on review of critical study site documentation and source data. These activities could be used to get information on the clinical study progress, to exchange information on the resolution of problems, review of procedures, study subject status as well as to facilitate remote site selection and investigator training for critical study procedures.

Risk Mitigation

- The Sponsor will continually assess whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to study subjects, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

APPENDIX 10. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The terms IP and study drug are used interchangeably throughout this document.

LIST OF ABBREVIATIONS	DEFINITIONS OF TERMS
5-ASA	5-aminosalicylate
ADME	absorption, distribution, metabolism, elimination
AE	adverse event
ALT	alanine aminotransferase
anti-TNF	anti-tumor necrosis factor
AST	aspartate aminotransferase
AUC	area under the drug concentration versus time curve
$AUC_{(0-\tau)}$	area under the curve during a dose interval
BID	twice per day
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CL/F	total body clearance corrected for bioavailability
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	chronic kidney disease epidemiology collaboration
CMC	carboxy methyl cellulose
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CPK	creatine phosphokinase
CRP	c-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DR	delayed-release or gastro-resistant
DRC	Data Review Committee
DSS	dextran sulfate sodium
ECG	electrocardiogram

LIST OF ABBREVIATIONS	DEFINITIONS OF TERMS
eCRF	electronic case report form
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EPO	erythropoietin
ET	early termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HDPE	high-density polyethylene
HIF	hypoxia inducible factor
HIF-1α	hypoxia inducible factor 1 alpha
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPβCD	2-hydroxypropyl-beta-cyclodextrin
HRT	hormone replacement therapy
IB	Investigator's brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	Immunoglobulin M
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MAD	multiple ascending dose

LIST OF ABBREVIATIONS	DEFINITIONS OF TERMS
MMX	multi-matrix
NASH	non-alcoholic steatohepatitis
NOAEL	no observed adverse effect level
NSAID	non-steroidal anti-inflammatory agents
OLE	open-label extension
OTC	over-the-counter
PCP	placebo-controlled period
PD	pharmacodynamics
PGA	Physician's Global Assessment
PGx	pharmacogenetics
PHD	prolyl hydroxylase
PHDi	prolyl hydroxylase inhibitor
PK	pharmacokinetic
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RHI	Robarts Histopathology Index
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SNP	single nucleotide polymorphism
SoA	Schedule of Activities
SNP	single nucleotide polymorphism
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	apparent terminal half-life
T_{max}	time of occurrence of maximum observed concentration
TE	target engagement
TEAE	treatment-emergent adverse events
TNBS	trinitrobenzene sulfonic acid
TNF-α	tumor necrosis factor alpha
UC	ulcerative colitis
UC-100 Index	Ulcerative colitis 100 index

LIST OF ABBREVIATIONS	DEFINITIONS OF TERMS
UGT	uridine-diphosphoglucuronosyl transferase
ULN	upper limit of normal
Vd/F	oral apparent volume of distribution corrected for bioavailability
VEGF	vascular endothelial growth factor
WBC	white blood cells
WOCBP	women of childbearing potential

APPENDIX 11. PROTOCOL AMENDMENT HISTORY

Amendment 1.0 (v2.0, 21 October 2020)

Overall Rationale for the Amendment:

The rationale for changes in this amendment includes primarily updates that extend the duration of the placebo-control period of the study and incorporate an open-label extension.

Table 1: Summary of Changes

Section # and Name	Description of Change	Brief Rationale
Global change affecting all protocol sections, including, but not limited to: 1 Protocol summary 3 Objectives/endpoints 4 Study design 5 Eligibility criteria 6 Investigational product 7 Discontinuation of IP 8. Study procedures 9 Statistical consideration	Extend the duration of placebo-controlled period (PCP) to 36 weeks and add a 24-week open-label extension	To evaluate the benefit-risk profile of GB004 compared to placebo with longer term dosing up to 36 weeks in terms of efficacy, safety, and tolerability, and to obtain further safety experience with the higher dose of GB004 (BID) in an open-label extension study
1.1 Protocol synopsis 1.3.1 SoA 4.1 Overall study design	Extend duration of screening period to 5 weeks	To provide adequate time to complete all screening assessments
2.3.2 Risk assessment	Update risks	To reflect emerging data and to align with the investigator's brochure
5.1 Inclusion criteria	• Clarify age for inclusion • Add beclomethasone as allowed UC background therapy	• To comply with different country regulations • To expand list of permitted background steroid therapy
5.2 Exclusion criteria	Exclude pregnant/lactating women	To reflect that pregnant/lactating women should be excluded
5.3 UC disease activity criteria Appendix 8 Instructions for calculating Mayo score for UC disease activity criteria assessment	Add sections	Part of modifying the study design (mentioned above)
6.5.2 Background UC therapy	Add tapering instructions for systemic steroids after PCP Week 12	Part of modifying the study design (mentioned above)

Section # and Name	Description of Change	Brief Rationale
6.8 Concomitant therapy	Delete section on CYP3A4	Per emerging in vitro data suggesting that GB004 and its glucuronide metabolite have a low potential to inhibit CYP3A4 substrates
8.1.3 RHI Score, Geboes Score and UC Index-100	Add RHI calculation	For clarity
8.2.1 Physical examination	Clarify and differentiate between complete and symptom-directed physical examination	For clarity
Appendix 9 Guidance to address a pandemic or other global health emergencies	Update	To reflect updated guidance by regulatory agencies
General	Minor clarifications throughout protocol Update list of abbreviations, formatting, hyperlinks	For consistency and accuracy throughout protocol

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