CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, multi-center study to evaluate the efficacy and safety of GB001 as maintenance therapy in adult subjects with moderate to severe asthma
Short Title:	GB001 in adult subjects with moderate to severe asthma
Protocol Number:	GB001-2001
Compound Number:	GB001
Study Phase:	Phase 2b
Sponsor Name:	GB001, Inc., a wholly owned subsidiary of Gossamer Bio, Inc.
Legal Registered Address:	3013 Science Park Road, Suite 200 San Diego, CA 92121, USA
Regulatory Agency Identifier Number(s):	[redacted] **EudraCT:** 2018-002242-36
Version:	5.0
Approval Date:	16 Apr 2020

SPONSOR'S AUTHORIZED REPRESENTATIVE SIGNATURE PAGE

[redacted]

Gossamer Bio Services, Inc. on behalf of GB001, Inc, a wholly owned subsidiary of Gossamer Bio, Inc.

Medical Monitor Name and Contact Information will be provided separately.

INVESTIGATOR AGREEMENT

GB001-2001: A Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, multi-center study to evaluate the efficacy and safety of GB001 as maintenance therapy in adult subjects with moderate to severe asthma

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, 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 GB001, Inc.

_____

Signature

_____ _____

Name of Investigator Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4 (v5.0)	16-Apr-2020
Amendment 3 (v4.0)	18-Feb-2020
Amendment 2 (v3.0)	28-Aug-2019
Amendment 1 (v2.0.0)	28-Feb-2019
Original Protocol (v1.0.0)	02-Aug-2018

Amendment 4 (v5.0; 16 Apr 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to enhance monitoring of liver parameters during the conduct of the trial and to provide guidance to address a pandemic or other global health emergencies.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.1 GB001 Benefit/Risk Assessment	Updated assessment with recent data	Updated to clarify risk of liver injury, critical need for liver monitoring, and low threshold for stopping study drug in cases of suspected liver injury
[redacted]	[redacted]	[redacted]
Section 10.6 Appendix 6: Liver Safety - Actions and Follow-up Assessments	Added actions (discontinuation of IP) if labs are not able to be confirmed within 48 hours and steps for management of IP re-challenges	Clarified discontinuation of IP if repeat labs could not be obtained within 48 hours and conditions for re-challenge with investigational product in the case of adverse events of interest
Section 10.12 Appendix 12: Guidance to Address a Pandemic or Other Global Health Emergencies and Potential Impact on the Clinical Study	Added language to address global health emergencies, eg, COVID-19	Clarified that certain adjustments to the protocol may be made in line with Regulatory Authorities Guidance in order to ensure the safety of subjects, maintaining

Section # and Name	Description of Change	Brief Rationale
		compliance with good clinical practice (GCP), and minimizing the risks to trial integrity during the COVID-19 pandemic
Global Change	Minor revisions to text	Administrative clarifications were incorporated, and typographical errors were corrected

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, multi-center study to evaluate the efficacy and safety of GB001 as maintenance therapy in adult subjects with moderate to severe asthma

Short Title: GB001 in adult subjects with moderate to severe asthma

Rationale:

GB001 is a potent and highly selective oral prostaglandin D_2 receptor (DP_2) antagonist. DP_2 is expressed on a variety of cells implicated in the allergic process including eosinophils and epithelial cells (Kupczyk, 2017; Singh, 2017). GB001 is being developed as a once daily oral add-on maintenance treatment for moderate to severe eosinophilic asthma.

The purpose of this Phase 2b study is to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of 3 GB001 dose levels compared with placebo in subjects with moderate to severe asthma and an eosinophilic phenotype. The study will assess the efficacy of GB001 relative to placebo in reducing asthma worsening when added to standard of care (SOC) asthma maintenance therapy.

Objectives and Endpoints (Primary and Secondary):

Objectives	Endpoints
Primary	
• To evaluate the effect of GB001 compared to placebo on reducing asthma worsening	• The proportion of subjects who experience worsening of asthma by Week 24 as defined by at least one of the following: o On 2 consecutive days, morning (AM) peak expiratory flow (PEF) ≤ 75% of mean AM PEF measured over the last 7 days of the Run-in o Forced expiratory volume in 1 second (FEV_1) < 80% of baseline (Visit 2) o Increase in rescue medication use of ≥ 6 puffs/day on 2 consecutive days compared to mean use over the last 7 days of the Run-in o Increase in Asthma Control Questionnaire (ACQ-5) score of ≥ 0.5 compared to baseline (Visit 2) o The occurrence of a severe asthma exacerbation (asthma attack) defined as deterioration of asthma that leads to the use of systemic corticosteroids for at least 3 days, hospitalization, or an Emergency Department visit
Secondary	
• To evaluate the effects of GB001 compared with placebo on a range of clinical endpoints, including change in ACQ-5 score, change in pulmonary function, and time to first asthma worsening event	• Change from baseline to Week 24 in ACQ-5 score • Change from baseline to Week 24 in pre-bronchodilator FEV_1 • Time to first asthma worsening • Annualized rate of severe asthma exacerbations • Change from baseline to Week 24 in post-bronchodilator FEV_1 • Change from baseline to Week 24 in AM PEF
• To evaluate the safety and tolerability of GB001 compared with placebo	• Incidence of treatment-emergent adverse events (TEAEs) • Change from baseline in laboratory, vital signs, and electrocardiogram (ECG) parameters

Overall Design:

This is a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, multi-center study to evaluate the efficacy and safety of GB001 as maintenance therapy in a moderate to severe eosinophilic asthma population. GB001 will be added to the subject's standard-of-care asthma treatment.

An interim analysis to inform further development of GB001 will be conducted after the first 320 subjects have completed the study or have prematurely withdrawn from the study.

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

Disclosure Statement:

This is a parallel group treatment study with 4 arms that is participant, Investigator, and Sponsor blinded.

Number of Participants:

This study will randomize approximately 480 subjects, with approximately 120 subjects per treatment group.

Intervention Groups and Duration:

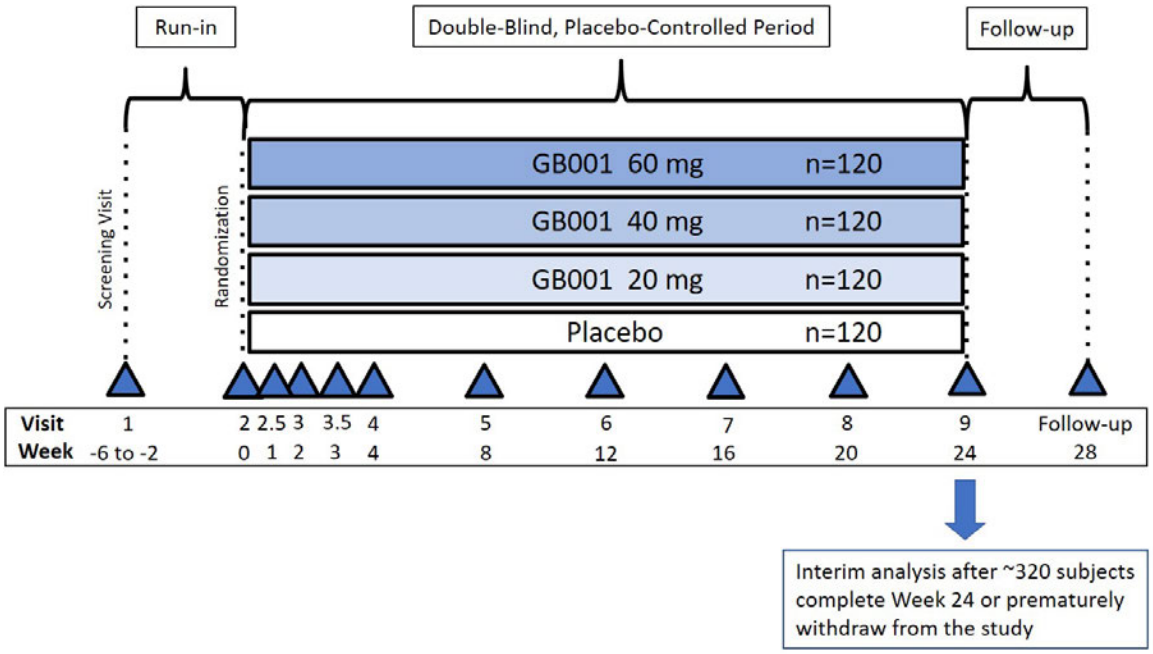
Treatment groups:

- GB001 60 mg daily
- GB001 40 mg daily
- GB001 20 mg daily
- Matching placebo daily

Total duration for study participation per subject is up to 34 weeks (includes a Screening visit; followed by a 2-week to 6-week Run-in period to allow for collection of baseline eDiary data; a 24-week Double-Blind, Placebo-Controlled period; and 4-week Follow-up period).

Independent Data Monitoring Committee (IDMC): Yes

1.2. Schema


Run-in
Double-Blind, Placebo-Controlled Period
Follow-up
Screening Visit
Randomization
GB001 60 mg n=120
GB001 40 mg n=120
GB001 20 mg n=120
Placebo n=120
Visit 1 2 2.5 3 3.5 4 5 6 7 8 9 Follow-up
Week -6 to -2 0 1 2 3 4 8 12 16 20 24 28
Interim analysis after ~320 subjects complete Week 24 or prematurely withdraw from the study

1.3. Schedule of Activities

Procedure	Screening Visit	Randomization	Double-Blind, Placebo-Controlled Period Visit Window is ± 2 days									Early Discontinuation of IP	Early Withdrawal from Study	Follow-up (after W24 or 4 weeks after EW from study)	Notes
Visit	**1**	**2**	**2.5**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**	If needed	If needed	**Follow-up**	
Week	**-6 to -2**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	If needed	If needed	**28**	
Written informed consent	X*														*May be obtained prior to Visit 1
Demography	X														
Medical history	X														Including atopic conditions
Asthma and exacerbation history	X														Including triggers
Asthma treatment history	X														
Smoking history	X														
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Including SOC asthma treatment
Complete physical examination	X										X	X	X		Including height and weight. Conduct prior to spirometry.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead electrocardiogram	X							X			X	X	X		Prior to spirometry
Fractional exhaled nitric oxide	X	X						X			X	X	X		Prior to spirometry. Prior to exhaled breath condensate analysis, if performed. See Section 8.6.2.
Exhaled Breath Condensate Analysis		X *									X	X			May be collected at sites that are properly trained and qualified. Prior to spirometry. *Exhaled breath condensate analysis may be conducted on the next calendar day. See Section 8.6.7.
Spirometry pre-bronchodilator	X	X				X	X	X	X	X	X	X	X	X	
Spirometry post-bronchodilator	X										X	X			After 4 puffs albuterol/salbutamol
Inclusion/exclusion criteria	X														
Randomization criteria		X													
Asthma Control Questionnaire-5	X	X		X		X	X	X	X	X	X	X	X	X	

Procedure	Screening Visit	Randomization	Double-Blind, Placebo-Controlled Period Visit Window is ± 2 days									Early Discontinuation of IP	Early Withdrawal from Study	Follow-up (after W24 or 4 weeks after EW from study)	Notes
Visit	**1**	**2**	**2.5**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**	If needed	If needed	**Follow-up**	
Week	**-6 to -2**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	If needed	If needed	**28**	
Asthma Quality of Life Questionnaire-(Standardized)		X									X	X	X		
Sino-Nasal Outcome Test-22		X									X	X	X		Only in subjects with a history of sinusitis or allergic rhinitis
Hair loss assessment		X									X	X	X		See Section 8.1.7
Pregnancy test (women of child-bearing potential only)	S	U		U		U	U	U	U	U	U	U	U	U	S = Serum U = Urine. If urine is positive, collect serum to confirm.
Hematology with differential	X	X *				X		X			X	X	X	X	See Appendix 2 (Section 10.2) *Includes INR at Visit 2.
Total IgE		X													
Clinical chemistry	X	X						X			X	X	X		See Appendix 2 (Section 10.2). Clinical chemistry includes liver chemistry.
Liver chemistry	X	X *	X	X	X	X *	X *	X *	X	X	X	X	X	X	See Appendix 2 (Section 10.2) Table 3 and Appendix 6 (Section 10.6) Includes total bile acid at every visit. *If ALP > 1xULN, collect fractionation of ALP at every visit
Urine cotinine	X	X									X	X	X		
Urinalysis	X										X	X	X		See Appendix 2 (Section 10.2)

Procedure	Screening Visit	Randomization	Double-Blind, Placebo-Controlled Period Visit Window is ± 2 days									Early Discontinuation of IP	Early Withdrawal from Study	Follow-up (after W24 or 4 weeks after EW from study)	Notes
Visit	**1**	**2**	**2.5**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**	If needed	If needed	**Follow-up**	
Week	**-6 to -2**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	If needed	If needed	**28**	
Hepatitis B surface antigen and Hepatitis C antibody	X														If Hepatitis C test is positive or indeterminate, a confirmatory test will be reflexively performed to confirm the results
Pharmacokinetic sample pre and post in-clinic dosing		X *													See Section 8.5 *predose and 2.5 hours postdose
Pharmacokinetic sample				X				X		X	X	X	X		Subject to record time of dose taken at home in the prior evening. See Section 8.5
At-home RNA Transcriptome Research										D	R				D = dispense, R = return See Section 8.6.3
At-site RNA Transcriptome Research	X	X		X							X*	X*	X		*At end of IP (Visit 9 or Early Discontinuation of IP visit, as applicable) See Section 8.6.3
Biomarker sample (blood, urine, airway)		X *		X							X	X			See Sections 8.6.4, 8.6.5, and 8.6.6 *predose and 2.5 hours postdose
Nasal sample		X		X							X	X			Collected in all subjects. V2: pre- and post-dose sample collection
Sputum eosinophil and neutrophil		X *									X	X			May be collected at sites that are properly trained and qualified. Section 8.6.1 *Sputum analysis and first dose may be conducted on the next calendar day, after other V2 procedures

Procedure	Screening Visit	Randomization	Double-Blind, Placebo-Controlled Period Visit Window is ± 2 days									Early Discontinuation of IP	Early Withdrawal from Study	Follow-up (after W24 or 4 weeks after EW from study)	Notes
Visit	**1**	**2**	**2.5**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**	If needed	If needed	**Follow-up**	
Week	**-6 to -2**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	If needed	If needed	**28**	
Pharmacogenetic sample		X *		*		*	*	*	*	*	*	*			*If consent provided, samples can be collected at any visit post-randomization; see Section 8.7 and Appendix 5 (Section 10.5)
Asthma worsening review		X		X		X	X	X	X	X	X	X	X	X	to include assessment of severe asthma exacerbation
Download and review eDiary		X		X		X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Including review for liver events
Dispense investigational product (IP)		X		X		X	X	X	X	X					If subject discontinues IP, but stays on study, do not dispense IP at subsequent visits (Section 7.1)
Collect used IP/conduct accountability				X		X	X	X	X	X	X	X	X		
Verify subject has rescue inhaler	X	X		X		X	X	X	X	X					
Dispense eDiary, if all screening eligibility criteria are met	X														Eligible subjects enter Run-in period and complete eDiary
Collect eDiary													X	X	
Register visit with Interactive Response Technology system	X	X		X		X	X	X	X	X	X	X	X	X	
Complete case report form (eCRF)	X	X		X		X	X	X	X	X	X	X	X	X	

Abbreviations: EW = early withdrawal; IP = investigational product

2. INTRODUCTION

2.1. Study Rationale

GB001 is a potent and highly selective oral prostaglandin D_2 receptor (DP_2) antagonist. DP_2 is expressed on a variety of cells implicated in the allergic process including eosinophils and epithelial cells (Kupczyk, 2017; Singh, 2017). GB001 is being developed as a once daily oral add-on maintenance treatment for moderate to severe eosinophilic asthma.

The purpose of this Phase 2b study is to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of 3 GB001 dose levels compared with placebo in subjects with moderate to severe asthma and an eosinophilic phenotype. The study will assess the efficacy of GB001 relative to placebo in reducing asthma worsening when added to standard of care (SOC) asthma maintenance therapy.

2.2. Background

More than 300 million people around the globe are diagnosed with asthma, a heterogenous chronic disease characterized by variable airflow obstruction and symptoms of cough, wheeze, and dyspnea. Inhaled corticosteroids (ICS) are the cornerstone of asthma maintenance therapy, with or without additional controllers (GINA, 2018). However, not all patients have a complete resolution of the underlying inflammation, and some continue to have severe asthma exacerbations. Prevention of severe asthma exacerbations is of utmost importance in the treatment of asthma. The significance of preventing severe asthma exacerbations is highlighted as 1 of the 7 key conclusions in the recent Lancet Commission Report (Pavord, 2018). Severe exacerbations create anxiety for the patient and their families, place stress on the healthcare system, and may result in more rapid decline in lung function (Reddel, 2009; O'Byrne, 2011; Ortega, 2018). From a societal perspective, asthma exacerbations result in millions of days of lost work each year (Botturi, 2011; Catley, 2011). The occurrence of asthma worsening or severe asthma exacerbations (asthma attack) is not infrequent. Approximately 45% of working adults in the United States with a diagnosis of asthma experienced at least one episode over the 5-year period from 2011-2016 (Mazurek, 2018). In summary, there continues to be an unmet medical need to provide novel therapies to reduce asthma worsening and severe asthma exacerbations.

New biologics have recently entered the market to address, in part, the unmet medical need. However, these medications are given by injection, which currently requires a patient to visit a clinic every 2 to 8 weeks and may require multiple injections per dose. In addition, these medications may not be available to every patient who needs them. Lastly, biologic medications are restricted to patients who require Global Initiative for Asthma (GINA) guideline step 5 treatment (GINA, 2018) and have exhausted other asthma therapies. It would be beneficial to have an effective therapy for reducing severe exacerbations as an option at earlier GINA steps.

The class of compounds known as DP_2 antagonists which act through the DP_2 receptor may offer the potential to become an add-on oral maintenance therapy at GINA step 4 or earlier to decrease the occurrence of asthma exacerbations. DP_2 has been implicated as a pathway that has a direct effect upon specific cell types that are associated with severe asthma, specifically mast cells and eosinophils. Importantly, it has been demonstrated that asthma patients with more severe disease

or a history of an exacerbation in the prior year had upregulation of the prostaglandin D_2 (PGD_2)-DP_2 pathway and had the highest expression of the DP_2 receptor in bronchial biopsy samples (Fajt, 2013). It is anticipated that GB001 will reduce recruitment and activation of airway eosinophils, with consequent reduction in airway inflammation including effects on fractional exhaled nitric oxide (FeNO). In a recent post-hoc analysis of 36 subjects (ADC3680-04) with mild to moderate atopic asthma receiving a total daily dose of fluticasone propionate ≤ 500 µg or equivalent, who were randomized (2:1) to 30 mg of GB001 or placebo once daily for 28 days, lung function was analyzed by baseline FeNO (< 35 and ≥ 35 ppb) and blood eosinophil (< 200 and ≥ 200/µL) subgroups (Ortega, 2019a; Ortega, 2019b). In the overall population, GB001 had a favorable effect on forced expiratory volume in 1 second (FEV_1) at Day 28 (difference in mean change for GB001 versus placebo of 102 mL, n = 36). Changes in FEV_1 were also observed in the high baseline FeNO (n = 14) and high baseline eosinophil (n = 16) subgroups (differences of 207 mL and 81 mL, respectively). These results suggest that GB001 favorably influences lung function in subjects with markers of eosinophilic inflammation.

Two important studies with the oral DP_2 antagonist fevipiprant provide further support for the development of this class of compounds for the reduction of asthma exacerbations in patients with severe asthma and markers of eosinophilic inflammation. In the first study conducted by Gonem et al, fevipiprant (compared to placebo) significantly reduced eosinophilic inflammation as measured by a reduction in sputum eosinophils in patients receiving ICS and having either an ACQ-7 score of at least 1.5 at randomization or a severe asthma exacerbation in the prior year (Gonem, 2016). The magnitude of reduction in sputum eosinophils with fevipiprant treatment for 12 weeks is consistent with that of the biologic mepolizumab (Haldar, 2009; Pavord, 2012). The second Phase 2 study is a large dose-ranging study that evaluated the effect of a wide range of fevipiprant doses in comparison to placebo and montelukast in a population with moderate to severe asthma. The primary efficacy outcomes were based upon FEV_1 which demonstrated improvements in lung function from baseline over 12 weeks. Additionally, a post-hoc analysis investigated the reduction in asthma worsening/exacerbations in over 1000 patients. Despite the short treatment duration of 12 weeks, a trend for reduction of asthma worsening and asthma exacerbation events was seen when all doses (1 mg to 450 mg) were pooled (Bateman, 2017).

The effect of GB001 in reducing asthma worsening has been studied in a Phase 2 study in Japanese subjects (Study PTR-36-201). This study enrolled subjects who were taking a medium-dose ICS or medium-dose ICS/LABA. Prior to start of the Run-in, subjects taking ICS/ long-acting beta agonist (LABA) were required to switch to ICS only. At baseline, subjects evaluated for efficacy had a mean ACQ score of 0.795 and a mean eosinophil count of 319 cells/µL. Following a Run-in period, subjects were randomized to double-blind treatment with GB001 20 mg, GB001 5 mg, or placebo for 16 weeks. During the first 8 weeks on study (ie, 4-week Run-in and 4 weeks of the double-blind treatment period), background ICS treatment was tapered and ultimately withdrawn. Subjects then continued for an additional 12 weeks on monotherapy. The proportion of subjects with asthma worsening was significantly lower in the 2 GB001 groups (32.7% GB001 5 mg, 20.8% GB001 20 mg) compared with the placebo group proportion of 52.8% ($p < 0.05$ for both dose levels). Collectively, these data along with the data from fevipiprant support further investigation of GB001 to reduce asthma exacerbations.

The results of other GB001 clinical studies are available in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

2.3.1. GB001 Risk/Benefit Assessment

GB001, an oral DP_2 antagonist, is being developed as a maintenance therapy in asthma. Despite the recent availability of injectable biologics to manage asthma patients with poor control and exacerbations, there continues to be a paucity of oral agents to help manage and control asthma. The mechanism of GB001 is to antagonize the DP_2 receptor and thereby reduce the T helper cell type 2 (Th2) response while affecting other cells relevant in the inflammatory and allergic cascade with corresponding improvements in asthma control, lung function and exacerbations (Hall, 2015; Gonem, 2016; Bateman, 2017). Ultimately these physiologic effects could result in an improvement in the overall quality of life of patients with moderate to severe asthma.

As of 29 August 2019, a total of 459 subjects have received at least 1 dose of GB001 at any dose level. Drug induced liver injury is considered a potential risk of GB001 due to the occurrence of two Hy's Law cases, one was a liver disorder (preferred term) in a healthy subject at 160 mg in Study PTR-36-101 and one was hepatic enzyme increased (preferred term) in the current study which remains blinded. Details are provided in the IB. Liver monitoring is critical for the safe management of subjects. Investigators should have a low threshold for discontinuing study drug with any suspicion of drug-induced liver injury. Safety will be closely monitored by the Sponsor and the Independent Data Monitoring Committee (IDMC).

2.3.2. Study Design Risk/Benefit Assessment

This study is designed to assess the effect of GB001 on asthma worsening, while maintaining asthma controller therapy. Since this study employs an add-on therapy design, subjects will be maintained on their stable SOC regimen throughout the study.

To minimize the potential risk to subjects, stringent criteria are utilized during screening to exclude subjects with a history of significant other pulmonary disease, liver disease or other comorbidities that could impact subjects' safety. In addition, subjects will be closely monitored with regards to liver function following current guidelines. All subjects will be closely monitored throughout the study through daily home morning peak expiratory flow (PEF) and eDiary monitoring. Alerts are programmed into the eDiary that trigger in the event of potential loss of asthma control. Upon receiving an alert, subjects will be instructed to contact their study physician and if necessary go to the site for further evaluation.

Exacerbations are recognized as a common clinical manifestation in patients with severe asthma (GINA, 2018). Currently, management of acute exacerbations includes high doses of systemic corticosteroids, which is coupled with the known health risks associated with steroids (Dalal, 2016). This study offers the potential benefit for subjects receiving GB001 to experience fewer exacerbations and consequently have a reduction in the total cumulative dose of systemic corticosteroids (eg, prednisone), thereby minimizing the risk of acute systemic side effects of corticosteroids. As an additional potential benefit, all participating subjects on active or placebo will be frequently and closely monitored during the duration of the study with optimized standard of care. Furthermore, in patients who complete the study, an extension follow-up study may be offered in which all subjects will receive GB001.

The current study proposes to minimize the number of subjects to be exposed to GB001, while still being able to assess potential effects on asthma worsening and exacerbations. Based upon the study design and the close monitoring from both the Sponsor and the IDMC, the benefits of participation in GB001-2001 outweigh the potential risks of exposure to GB001.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of GB001 compared to placebo on reducing asthma worsening	• The proportion of subjects who experience worsening of asthma by Week 24 as defined by at least one of the following: o On 2 consecutive days, morning (AM) peak expiratory flow (PEF) ≤ 75% of mean AM PEF measured over the last 7 days of the Run-in o Forced expiratory volume in 1 second (FEV_1) < 80% of baseline (Visit 2) o Increase in rescue medication use of ≥ 6 puffs/day on 2 consecutive days compared to mean use over the last 7 days of the Run-in o Increase in Asthma Control Questionnaire (ACQ-5) score of ≥ 0.5 compared to baseline (Visit 2) o The occurrence of a severe asthma exacerbation (asthma attack) defined as deterioration of asthma that leads to the use of systemic corticosteroids for at least 3 days, hospitalization, or an Emergency Department visit
Secondary	
• To evaluate the effects of GB001 compared with placebo on a range of clinical endpoints, including change in ACQ-5 score, change in pulmonary function, and time to first asthma worsening event	• Change from baseline to Week 24 in ACQ-5 score • Change from baseline to Week 24 in pre-bronchodilator FEV_1 • Time to first asthma worsening • Annualized rate of severe asthma exacerbations • Change from baseline to Week 24 in post-bronchodilator FEV_1 • Change from baseline to Week 24 in AM PEF

• To evaluate the safety and tolerability of GB001 compared with placebo	• Incidence of treatment-emergent adverse events (TEAEs) • Change from baseline in laboratory, vital signs, and electrocardiogram (ECG) parameters
Tertiary/Exploratory	
• To evaluate the effect of GB001 compared to placebo on patient reported outcomes (PRO)	• Proportion of subjects with a greater than or equal to 0.5 decrease in ACQ-5 score from baseline • Change from baseline in Asthma Quality of Life Questionnaire-Standardized (AQLQ-S) • Change from baseline in Sino-Nasal Outcome Test (SNOT-22) • Change from baseline in hair-loss assessment
• To evaluate the effects of GB001 on additional markers of asthma control	• Change from baseline in daily salbutamol/albuterol use • Change from baseline in daily asthma symptom scores • Change from baseline in awakening at night due to asthma symptoms requiring rescue medication use
• To evaluate the pharmacokinetics (PK) of GB001	• Pharmacokinetics in plasma
• To characterize target engagement, biomarkers and pharmacodynamic (PD) profile of GB001	• Change from baseline in target engagement, biomarkers and other pharmacodynamic parameters (may include blood, urine, and airway)

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, multi-center study to evaluate the efficacy and safety of GB001 as maintenance therapy in a moderate to severe eosinophilic asthma population. GB001 will be added to the subject's standard-of-care asthma treatment.

An interim analysis to inform further development of GB001 will be conducted after the first 320 subjects have completed the study or have prematurely withdrawn from the study (see Section 9.5).

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

4.1.1. Study Design

The study will commence with a Screening visit (Visit 1), at which informed consent will be obtained and inclusion and exclusion criteria will be assessed. Informed consent may be obtained prior to the day of the Screening visit to allow for medication washouts or for other logistical reasons such as obtaining documentation of exacerbations or historical reversibility, if necessary. All other screening procedures should be completed on the day of the Screening visit. Subjects not meeting the eligibility criteria will be deemed screen failures and will not continue participation in the study (see Section 5.4). Eligible subjects will enter a Run-in period of a minimum of 2 weeks and a maximum of 6 weeks and will remain on their SOC regimen. The Run-in period commences with completion of all Screening visit procedures and concludes at the Randomization visit. During the Run-in period, subjects will capture PEF and asthma symptoms in an eDiary daily. Subjects who experience an asthma exacerbation during the Run-in period will receive appropriate treatment and remain in the Run-in period until their asthma status has returned to baseline status for at least 1 week. Subjects who are not able/eligible to be randomized due to ongoing asthma exacerbation at the end of the Run-in period will be discontinued from study participation and be labeled as Run-in failures. Subjects will remain on their SOC therapy during the Run-in period.

At Visit 2 (Week 0, Day 1), subjects who meet the randomization eligibility criteria will be randomized in a 1:1:1:1 ratio to receive one of the following double-blind treatments for 24 weeks:

- GB001 60 mg daily
- GB001 40 mg daily
- GB001 20 mg daily
- Matching placebo daily

Randomization will be stratified by baseline ICS dose (medium or high, as defined in Appendix 10; Section 10.10) and country.

The first dose of double-blind investigational product (IP) will be administered in the clinic on Day 1. All subsequent doses will be taken orally at home at bedtime on an empty stomach.

Following initiation of IP, subjects will visit the clinic for assessments at Weeks 2, 3, and 4, followed by visits approximately every 4 weeks for an additional 5 visits. Subjects should remain on their stable current SOC therapy (ie, medium or high dose ICS plus additional controller therapy) through the duration of their time on study (refer to Schedule of Activities, Section 1.3).

Subjects will be provided with an eDiary which is programmed to alert the subject of potential asthma worsening:

1. On 2 consecutive days, AM PEF ≤ 75% of mean AM PEF measured over the last 7 days of the Run-in period
2. Increase in rescue medication use of ≥ 6 puffs/day (last 24 hours) on 2 consecutive days compared to mean use over the last 7 days of the Run-in period
3. Nighttime awakening due to asthma symptoms requiring rescue medication for at least 2 of 3 successive nights
4. An asthma symptom score of 4 for at least 2 of 3 successive days.

Upon receiving an alert, the subject should contact the site staff as soon as practical to assess the subject's asthma status. The subject may be asked to return to the clinic when necessary to have their asthma status evaluated.

Subjects who permanently discontinue IP will be requested to attend the Early Discontinuation of IP visit and will be strongly encouraged to complete any remaining study visits as per the Schedule of Activities (SoA; Section 1.3). Subjects who permanently discontinue IP and continue in the study will complete the Early Discontinuation of IP visit at the time of IP discontinuation and then return for the next visit in the Double-Blind, Placebo-Controlled visit sequence. At the visits subsequent to the Early Discontinuation of IP visit, study procedures will be completed except for dispensation/return of IP. Subjects who withdraw from the study, regardless of the reason, will be requested to return to the clinic to complete the Early Withdrawal (EW) from Study visit. All subjects who remain on IP through and including Visit 9 (Week 24) or who complete the EW from Study visit will be asked to return for a Follow-up visit approximately 4 weeks after their last dose of IP to assess subject safety.

Total duration for study participation per subject is up to 34 weeks (includes a Screening visit, followed by a 2-week to 6-week Run-in period to allow for collection of baseline eDiary data; a 24-week Double-Blind, Placebo-Controlled period; and 4-week Follow-up period).

4.1.2. Unscheduled Visit

There may be a need to have a subject return to clinic for an unscheduled visit for a variety of reasons, including but not limited to: repeat of a lab test, replacement of IP kit, evaluation of an adverse event (AE), or evaluation of asthma status. Any procedure that is conducted during a regularly scheduled on-treatment visit may be performed at an unscheduled visit.

If a subject returns to the clinic between regularly scheduled visits to assess asthma status, the following should be conducted:

- Review eDiary data to confirm if asthma worsening has occurred; and
- Have the subject complete the ACQ-5 and spirometry if possible to determine if asthma worsening has occurred.

4.2. Scientific Rationale for Study Design

4.2.1. Study Population

The target population is patients with moderate to severe asthma who are currently receiving GINA step 4 or 5 therapy and have evidence of eosinophilic inflammation. Reducing eosinophilic inflammation within the lungs, assessed by measuring sputum eosinophils, has been associated with a reduction in asthma exacerbations (Haldar, 2009; Pavord, 2012). It is anticipated that GB001, as a DP_2 antagonist, will reduce sputum eosinophilia and consequently asthma exacerbations. As measurement of sputum eosinophils is cumbersome and requires sites experienced with this procedure to obtain appropriate samples, a surrogate measure of lung eosinophils, namely peripheral blood eosinophils, will be used in this study. The cut-off threshold of 250 cells/μL has been selected for this study as it is predicted to have a sensitivity of 84% and a specificity of 91% to differentiate less than versus ≥ 3% sputum eosinophils (Wagener, 2015).

Based upon regulatory guidance, patients with a history of asthma exacerbations should be recruited in studies where the primary endpoint is exacerbation reduction (EMA, 2015). Patients with a history of exacerbations are more likely to experience future exacerbations. Therefore, this study will be recruiting subjects with a history of at least 1 asthma exacerbation in the previous 12 months.

In addition, DP_2 antagonists might have an effect in a subset of subjects with inflammation beyond the lower airways such as upper airways and skin. Thus, exploratory assessments targeting these tissues will evaluate additional beneficial effects as a result of treatment with GB001.

4.2.2. Placebo Rationale

A placebo-controlled design is necessary because asthma is a disease that waxes and wanes over time, and the endpoint of asthma worsening has a subjective component. Therefore, it is important to be able to differentiate the efficacy of GB001 compared to the "placebo effect," which may be as high as 30% to 50% depending on the endpoint chosen (Castro, 2007). Importantly, placebo-controlled studies require fewer subjects than active-controlled studies to demonstrate superiority of the experimental treatment. In addition, comparisons between the GB001 and placebo treatment groups will facilitate differentiation of the GB001 safety profile from that of the subject's SOC therapy. Lastly, a placebo group, as opposed to an active control, will help to understand whether the occurrence of an AE in a GB001 group is different from that which would occur in the asthma population in the absence of GB001.

An IDMC will periodically convene to review unblinded efficacy and safety data. The first IDMC meeting at which results are reviewed will occur after approximately 50 subjects have been randomized and have completed 12 weeks on study or within 12 months of the first subject randomized.

A placebo-controlled design for this study is consistent with the European Medicines Agency regulatory guideline on the clinical investigation of IP for the treatment of asthma (EMA, 2015), wherein the following statement is made: "If the drug is not intended to be substituted for ICSs, add-on designs where the new drug is compared with placebo on top of standard background

medication are required." As such, GB001-2001 includes a placebo group in addition to the subject's SOC therapy.

4.2.3. Primary Endpoint Selection

The use of proportion of subjects with worsening of asthma as an endpoint has been employed successfully in previous asthma studies (Wenzel, 2013; Castro, 2014), including a Phase 2 study with GB001 (PTR-36-201). This composite endpoint has the potential to reduce the sample size and duration of a study relative to an endpoint of severe exacerbations, while providing a clinically meaningful output. At the same time, this allows fewer subjects to be exposed to an investigational product in development when the efficacy and safety have not been fully established. The parameters included in the asthma worsening composite endpoint include changes in lung function (FEV_1 and PEF), rescue medication use, asthma control and symptoms. These markers of asthma control are closely related to signs and symptoms associated to exacerbations.

4.3. Justification for Dose

This study will assess the dose-response relationship of 3 doses of GB001 (60 mg, 40 mg, and 20 mg) in adult subjects with moderate to severe asthma.

The GB001 40 mg dose was selected based on the anticipated pharmacokinetics (PK) and exposure levels extrapolated from the results of two Phase 2 studies with GB001 (Study PTR-36-201 and ADC3680-07) and based on prior efficacy and safety results from these studies. In Study PTR-36-201, GB001 20 mg and 5 mg doses were evaluated in an asthma treatment withdrawal design. Both doses of GB001 were effective in decreasing the proportion of subjects with asthma worsening/exacerbations as compared to placebo, with the 20 mg dose producing a larger treatment effect (20 mg: 20.8%; 5 mg: 32.7%; placebo: 52.8%). In addition, only the 20 mg dose demonstrated statistical significance for the endpoints of asthma control (ACQ-5) and time to asthma worsening relative to placebo. No improvements in lung function were observed, while less worsening of lung function was seen in the GB001 groups compared to placebo. A comparable safety profile was observed across all treatment arms (including placebo) in this study. Based on this data, the 40 mg dose has been selected for the current study.

To characterize the dose-response curve, 1 dose level below and 1 dose level above the 40 mg dose are included in the current study. The 20 mg dose has been included as a potentially suboptimal dose based on data generated from a Phase 2 study of GB001 versus placebo (Study ADC3680-07). This study found that GB001 20 mg daily produced some efficacy, as measured by improvements in ACQ scores, but this dose level did not result in improvements in lung function. The 60 mg dose is included to assess whether greater efficacy may be achieved beyond that of the 40 mg dose, since no improvements have been seen in lung function with lower doses to date.

4.4. End of Study Definition

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

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

5.1. Inclusion Criteria

To confirm eligibility, a review of each subject's medical records should be performed prior to the subject entering the Run-in period. Prior to randomization, additional randomization criteria (including blood eosinophils ≥ 250 cells/μL; Section 5.3) must be met.

Subjects are eligible to enter the Run-in period only if all the following criteria are met:

1. **Informed Consent:** Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. **Age:** ≥ 18 and < 75 years of age at the time of Screening visit.
3. **Gender:** Males or females:
   a. Women of childbearing potential (WOCBP) must use an acceptable method of contraception (see Appendix 4, Section 10.4) at least 1 month prior to Screening through 28 days after the last dose of IP.
4. **Weight:** at least 40 kg.
5. **Diagnosis of asthma:** A diagnosis of asthma by a physician according to GINA guidelines of at least 12 months prior to Screening.
6. **ICS plus additional controller:** Subjects with a documented requirement for regular treatment with medium or high dose ICS and at least one other controller medication for at least 12 months prior to Visit 1. Subjects must maintain a stable ICS dose regimen during the 4 weeks prior to Visit 1.
   a. Medium dose ICS is defined as an ICS dose equivalent to fluticasone propionate > 250 to 500 mcg/day and high dose is defined as an ICS dose equivalent to fluticasone propionate > 500 mcg/day (for equivalent ICS doses see Appendix 10, Section 10.10)
   b. An additional controller medication such as LABA, long-acting muscarinic antagonist (LAMA), or leukotriene receptor antagonist (LTRA).
7. **FEV_1**: a pre-bronchodilator FEV_1 of ≤ 85% of predicted normal.
8. **Reversibility/Airway Hyperresponsiveness**:
   - At least 12% in FEV_1 following 4 puffs of albuterol 400 μg ex-US (360 μg US) or 1 equivalent nebulized dose/salbutamol 100 mcg at Screening. Reversibility is to be assessed in all subjects at Screening.
   - If a subject does not reverse at least 12% at Screening, the site may submit historical documentation of one of the following for review and approval by the Medical Monitor:
     – reversibility in the 24 months prior to Screening visit, **OR**

- airway hyperresponsiveness demonstrated by a positive methacholine, histamine, or mannitol challenge.

9. **Evidence of uncontrolled asthma:** demonstration of uncontrolled asthma by one of the following:
   a. Previously confirmed history of 2 or more asthma exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to Screening visit.

      OR

   b. Previously confirmed history of 1 asthma exacerbation requiring treatment with systemic corticosteroids in the 12 months prior to Screening visit and ACQ-5 of ≥ 1.5 at Screening visit.
10. Are willing and able to comply with the requirements for participation in the study.

5.2. Exclusion Criteria

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

1. **Smoking history:** Current smokers (any substance), or former smokers with a smoking history of ≥ 10 pack-years [(number of cigarettes per day/20) x number of years smoked]. A former smoker is defined as a subject who quit smoking at least 6 months prior to Screening visit. This includes electronic cigarettes and vaping.
2. **Concurrent Respiratory Disease:** Presence of a known pre-existing clinically important lung condition other than asthma. This includes current infection, active tuberculosis infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer.
3. **Malignancy:** A current malignancy 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.)
4. **Liver Disease:** Known pre-existing liver disorders (ie, non-alcoholic fatty liver disease (NALFD) or Gilbert's syndrome), or unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices or persistent jaundice), cirrhosis, or known biliary abnormalities.
5. **Other Concurrent Medical Conditions:** Known, pre-existing clinically significant endocrine, autoimmune, metabolic, neurological, renal (calculated creatinine clearance < 60 mL/min), gastrointestinal, hepatic, cardiovascular, hematological, or any other system abnormalities that are uncontrolled with standard treatment.
6. **Eosinophilic Disease:** Subjects with any other condition that could lead to elevated eosinophils such as hypereosinophilic syndrome, including eosinophilic granulomatosis with polyangiitis.
7. **ECG Assessment:** QTcF ≥ 450 msec for males or QTcF ≥ 470 msec for females at the Screening visit. If QTcF is above the prespecified limit and there are no other clinically

significant abnormalities, the assessment can be repeated in triplicate and the three results will be averaged for eligibility.

8. **Alcohol/Substance Abuse:** A history or suspected history of alcohol misuse or substance abuse, including marijuana, within 12 months prior to Screening visit.
9. **Immunodeficiency:** A known immunodeficiency, including that due to human immunodeficiency virus (HIV), other than that explained by systemic corticosteroid use.
10. **Investigational medications:** Subjects who have received treatment with an investigational medication within the past 30 days or within 5 half-lives of the medication, whichever is longer, prior to Screening visit. (This also includes investigational formulations of marketed products.)
11. **DP_2 (CRTh2) antagonist studies:** Participated in another DP_2 (CRTh2) antagonist study in the 12 months prior to Screening visit or known prior intolerance or inadequate response in a prior DP_2 antagonist study.
12. **Receiving prohibited medications or treatments:** (refer to Appendix 8, Section 10.8, for more details)
    a. Regular use of systemic corticosteroids or immunosuppressive therapies including methotrexate or azathioprine
    b. Monoclonal antibodies used in the treatment of asthma such as reslizumab, mepolizumab, omalizumab or benralizumab
    c. Medications, food or drink that are moderate or strong CYP3A4 inhibitors or inducers
    d. Medications that have the potential for interaction with GB001
    e. Bronchial thermoplasty and radiotherapy are excluded in the 12 months prior to Screening
13. **Prior participation in a study with GB001:** Subjects who previously participated in a study with GB001 (also named PTR-36 or ADC3680) are not eligible for this study.
14. **Hypersensitivity:** A known sensitivity to GB001 or any of its excipients. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption are not eligible for this study. Subjects with mild-moderate lactose intolerance are not excluded.
15. **Pregnancy:** Subjects who are pregnant or breastfeeding. Subjects should not be enrolled if they are planning to become pregnant during the time of study participation. A serum pregnancy test is required of all females of child-bearing potential at Screening.
16. **Adherence:** Subjects who have a known lack of adherence to controller medications.
17. **Body Mass Index (BMI):** BMI is ≥ 40 kg/m^2.
18. Have any other condition or reason that, in the opinion of the Investigator, would prohibit the subject from participating in the study, including participation in another clinical trial while participating in this study.

5.3. Randomization Criteria

At the end of the Run-in period, study subjects must fulfill the following criteria to be randomized to study treatment:

1. **Eosinophilic asthma:** A peripheral blood eosinophil count of ≥ 250 cells/μL measured at the Screening visit. **NOTE:** In a subject with prior evidence of an eosinophilic phenotype, as assessed by the Investigator, an eosinophil count < 250 may be repeated during Run-in upon approval by the Medical Monitor.
2. **FEV_1:** The morning percent predicted FEV_1 must be ≤ 85% of the predicted normal at both the Screening visit and Randomization visit.
3. **FEV_1 overread:** The Screening visit overread by vendor must confirm eligibility was met.
4. **eDiary compliance:** Compliance with completion of the eDiary as defined as:
   - Completion of rescue medication use question on 4 or more of the last 7 days immediately prior to Visit 2 (includes the morning of Visit 2).

     AND

   - Completion of AM PEF on 4 or more of the last 7 mornings immediately prior to Visit 2 (includes the morning of Visit 2).
   - **Note:** If the eDiary was completed on < 4 days due to technical challenges, the Visit 2 may be delayed up to an additional 3 days to allow for completion of the eDiary parameters above.
5. **ACQ-5:** The ACQ-5 assessment has been completed in the eDiary in clinic during the Randomization visit.
6. **Laboratory abnormality:** No evidence of clinically significant abnormality in the hematological, biochemical, or urinalysis at Screening visit, as judged by the Investigator.
7. **Hepatitis status:** No evidence of chronic hepatitis B or C, as evidenced by a negative hepatitis B surface antigen (HbsAg) or hepatitis C test at the Screening visit. Note: if hepatitis C antibody test is positive or indeterminate at screening, the confirmatory test result must be negative for Hepatitis C.
8. Chemistry and hematology obtained at Screening visit:
   - ALT must be < 2x the upper limit of normal (ULN)
   - AST must be < 2x ULN
   - Alkaline phosphatase must be < 2x ULN
   - Bilirubin must be < 1x ULN
   - Absolute eosinophil count must be < 1,500 cells/μL
   - White blood cell count must be < 15,000 cells/μL

9. **ECG overread:** The screening ECG overread confirms the QTcF interval is < 450 msec for males or QTcF < 470 msec for females.
10. **Asthma exacerbation:**

    Subjects who experience an asthma exacerbation during the Run-in period should have their Randomization visit (Visit 2) delayed until the Investigator considers the subject has returned to their baseline asthma status. If a 6-week Run-in period has elapsed before the subject is back to baseline status, then the subject will be considered a Run-in failure. An asthma exacerbation is defined as worsening of asthma requiring the use of systemic corticosteroids for at least 3 days, hospitalization, or an Emergency Department visit.
11. **Compliance with the subject's SOC asthma therapy as evidenced by:**

    - No changes in the dose or regimen of the Run-in asthma therapy (except for treatment of an asthma exacerbation).

      AND

    - Subjects must have demonstrated ≥ 75% compliance with their SOC therapy during Run-in.
12. **Pregnancy test:** For WOCBP, both the serum pregnancy test at the Screening visit and the urine pregnancy test at Visit 2 must be negative.

5.4. Screen or Run-In Failures

Subjects will be assigned a subject number at the time of signing the ICF. Subjects who do not enter the Run-in period will be labeled as Screen failures.

Subjects who enter the Run-in period but are not randomized will be designated as Run-in failures, even if they complete the Run-in period.

A minimal set of Screen failure/Run-in failure information is required to ensure transparent reporting of Screen/Run-in failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, Screen/Run-in failure details, eligibility criteria, and any serious adverse event (SAE).

Subjects who are not randomized may be eligible to rescreen upon approval by the Medical Monitor. A new subject number will be assigned if approved to rescreen.

6. INVESTIGATIONAL PRODUCT

Table 1: Investigational Product Formulation by Treatment Group

Treatment Groups	GB001 60 mg	GB001 40 mg	GB001 20 mg	Placebo
Dose Formulation	Film-Coated Tablet	Film-Coated Tablet	Film-Coated Tablet	Film-Coated Tablet
Unit Dose Strength(s)	3 x 20 mg tablet	2 x 20 mg tablet and 1 x placebo tablet	1 x 20 mg tablet and 2 x placebo tablet	3 x placebo tablet
Dosage Level(s)	60 mg at bedtime	40 mg at bedtime	20 mg at bedtime	Placebo at bedtime
Route of Administration and Instructions	Oral on an empty stomach	Oral on an empty stomach	Oral on an empty stomach	Oral on an empty stomach
Packaging and Labeling	GB001 and Placebo film-coated tablets will be packaged in blinded dosing kits. Each kit will consist of a labeled wallet containing 2 blister cards with 24 tablets each (ie, 48 tablets per kit), which will provide sufficient doses for 16 days of treatment (14 days + 2 days for the visit window). Individual kits have been packaged to deliver 3 tablets per day of the appropriate combination of 20 mg and placebo tablets as described in "unit dose strength" above. Subjects will receive 1 or 2 kits at each visit based on the timing of the subsequent visit. The kits will be labeled as required per country requirement.			
Storage Requirements	IP should be stored at room temperature (20 - 25°C) in the original packaging. Protect from moisture. IP stored at site will be maintained under controlled, temperature monitored conditions. Excursions between 15-30°C are permitted. Any other excursion from the required storage condition will be reported to the Sponsor as soon as practical.			

6.1. Preparation/Handling/Storage/Accountability

1. 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.
2. Only subjects enrolled in the study may receive IP and only authorized site staff may supply study medications. All study medication must be stored in a secure, 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.
3. 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).

4. Further guidance and information for the final disposition of IP are provided in the Pharmacy Manual.

6.2. Measures to Minimize Bias: Randomization and Blinding

6.2.1. Assignment of a Subject Number

At the Screening visit (Visit 1), a unique subject number will be assigned to a subject upon signing of the ICF.

6.2.2. Randomization

All subjects will be centrally randomized to IP treatment group using an Interactive Response Technology (IRT) embedded in the electronic data capture (EDC) system. Before the study is initiated, directions for use of the system will be provided to the sites.

Randomization will be stratified by baseline ICS dose (medium or high as defined in Appendix 10; Section 10.10) and country.

6.2.3. Assignment of Investigational Product Kit Numbers

IP will be dispensed at the study visits as summarized in SoA. At the Randomization visit, the EDC system will assign an IP kit number based on the subject's randomized treatment group.

For subsequent visits when IP is dispensed, the EDC system will assign new IP kit numbers based on the subject's randomized treatment group.

6.2.4. Unblinding of an Individual Subject

The EDC 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 an effort to contact the Sponsor to discuss unblinding a subject's treatment assignment, unless this could delay emergency medical 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 and electronic case report form (eCRF).

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.

Designated 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 and performance of bioanalytical analysis of PK concentrations.

[redacted]

[redacted]

6.3. Investigational Product Compliance

Subjects will receive 1 or 2 kits at each visit based on the timing of the subsequent visit. Subjects should complete the first 14 days of tablets in the first kit before starting the second, as applicable. For additional details refer to Study Reference Manual and Pharmacy Manual.

IP accountability will be assessed at each visit by counting returned tablets. The CRF may be used as a source for documenting the placement of the returned tablets (see Section 6.1). Deviation(s) from the prescribed dosage regimen will be evaluated per guidelines provided in the Study Reference Manual. Subjects who demonstrate poor IP compliance should be reeducated on the importance of taking their medications.

Guidance for Missed Dose(s)

If a dose is missed, subjects should be instructed to skip the missed dose and resume dosing at their next scheduled dosing time. Subjects should dose only from the 3 tablets indicated for the current day of dosing in the IP kit. No tablets from other dosing days should ever be taken to substitute for a dropped or missing tablet. For additional details refer to Study Reference Manual and Pharmacy Manual.

6.4. Concomitant Therapy

Subjects should remain on their current SOC therapy (ie, medium or high dose ICS plus additional controller therapy) through the duration of their time on study. If a subject experiences asthma worsening as defined in Section 4.1.1 or if a subject discontinues IP or withdraws from the study due to lack of efficacy, SOC therapy may be adjusted, as needed, at the discretion of the Investigator.

Any medication or vaccine (including over-the-counter 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 Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

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

Please refer to Appendix 8 (Section 10.8) for prohibited medications and other prohibited treatments.

6.4.2. Restricted Medications

Restricted medications are defined as medications which should be avoided, if possible; however, they are not prohibited during this study if stable for at least one month before screening. If such medications are required, consider switching to another medication in the class that is not restricted. Please refer to Appendix 9 (Section 10.9) for restricted medications.

6.4.3. Rescue Medicine

Subjects will be provided with albuterol/salbutamol for use as needed. The rescue medication will be locally sourced or reimbursed. Subjects are permitted to use the study-provided albuterol/salbutamol or any other short-acting bronchodilator. All rescue medication use is to be captured in the eDiary. For the purposes of data capture within the eDiary, one nebule should be captured as 4 puffs of rescue medication.

If the subject requires medication in addition to a short-acting bronchodilator for treating asthma symptoms, the subject should contact the study site for evaluation of their asthma status.

6.5. Dose Modification

Dose modifications of IP are not permitted. Subjects who are unable to tolerate their assigned dose of IP must be discontinued from IP.

6.6. Intervention After the End of the Study

Subjects who complete the study and meet the eligibility criteria for the Extension Study (ES) may be offered the opportunity to receive active treatment in the ES when the study is available.

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND SUBJECT WITHDRAWAL FROM THE STUDY

7.1. Discontinuation of Investigational Product

Permanent discontinuation of IP does not mean withdrawal from the study, and remaining study procedures should be completed as indicated by the study protocol. If study IP is permanently discontinued, the subject will be encouraged to remain in the study and continue to complete all study visits as per the SoA (Section 1.3). If a subject permanently discontinues IP prior to Visit 8 (Week 20) and remains in the study through Visit 9 (Week 24), the subject will not need to return for the Follow-up visit.

Sections 7.1.1 and 7.1.2 define mandatory criteria for permanent discontinuation of IP.

For subjects who simultaneously discontinue IP and withdraw from the study, the Early Discontinuation of IP visit procedures should be conducted, as shown in the SoA (Section 1.3), and a separate Early Withdrawal from Study visit is not needed. The subjects should be encouraged to return for the Follow-up visit.

7.1.1. QTc Stopping Criteria

Subjects must permanently discontinue IP if QTcF > 500 msec.

7.1.2. Pregnancy

A subject must permanently discontinue IP if the subject becomes pregnant. See Appendix 4 Section 10.4 and Section 8.3.4 for additional details.

The Early Discontinuation of IP visit procedures should be conducted, as shown in the SoA (Section 1.3), and a separate Early Withdrawal from Study visit is not needed.

7.2. Subject Withdrawal from the Study

A subject may withdraw or be withdrawn from the study for the following reasons:

- Physician decision
- AE
- Noncompliance with study drug
- Withdrawal by subject
- Study terminated by Sponsor
- Site terminated by Sponsor
- Lost to follow-up
- Lack of efficacy
- Pregnancy

The reason for subject withdrawal from the study will be recorded in the eCRF.

At the time of withdrawal from the study, if possible, an Early Withdrawal from Study visit should be conducted, as shown in the SoA (Section 1.3). See 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.

For subjects who simultaneously discontinue IP and withdraw from the study, the Early Discontinuation of IP visit procedures should be conducted, as shown in the SoA (Section 1.3), and a separate Early Withdrawal from Study visit is not needed. The subjects should be encouraged to return for the Follow-up visit.

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.

7.3. Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return 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:

- 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.
- The Sponsor may also attempt to ascertain vital status on subjects deemed lost to follow up.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor 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 (Section 1.3), is essential and required for study conduct.
- All screening and randomization evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a log to record details of all subjects screened to either confirm eligibility or record reasons for screening or Run-in failures, as applicable.

The suggested order of study procedures should be as follows. (Note: this list is not all inclusive. Review the SoA and the Study Reference Manual for additional guidance.)

Screening Visit (Visit 1): all procedures should be completed on the same day with the exception of the Informed Consent, which should be obtained prior to the Visit:

- Informed consent
- Demography
- Concomitant medications and medical history
- Vital signs
- Physical exam
- 12-lead electrocardiogram
- Fractional exhaled nitric oxide (FeNO)
- Spirometry pre and post bronchodilator

- Have subject complete the ACQ-5 within the eDiary and download the completed questionnaire PRIOR to the subject leaving the clinic
- Review of inclusion/exclusion criteria
- Collect urine and blood samples
- Record adverse events, if any
- Ensure subject has a rescue inhaler
- Dispense eDiary and train subject in its use
- Complete eCRF

Note: During the Run-in period, the site should review the vendor overread of the ECG and spirometry report and the laboratory results, including the blood eosinophil count. If the overread or laboratory results indicates that the subject is not eligible for randomization, the subject should be contacted to return all study provided materials to the site. However, in a subject with prior evidence of an eosinophilic phenotype, as assessed by the Investigator, an eosinophil count < 250 cells/µL may be repeated during Run-in upon approval by the Medical Monitor.

Randomization Visit (Visit 2): All procedures should be completed on the same day. Sputum induction and Exhaled Breath Condensate may be conducted on the next calendar day when necessary, followed by the first dose in clinic and post PK sample. Randomization should be performed on the day of first dose in clinic. (List is not all inclusive. Review the SoA and the Study Reference Manual for additional guidance.)

- Download the eDiary and check if today's diary has been completed
- Review eDiary to assess eligibility
- Review randomization eligibility criteria
- Have subject complete questionnaires
- Exacerbation review
- Concomitant medications and adverse event review
- Vital signs
- FeNO
- Exhaled breath condensate (EBC) analysis (only at select sites that are properly trained and qualified)
- Spirometry (pre-bronchodilator only)
- Collect lab samples and predose PK sample
- Sputum induction (only at select sites that are properly trained and qualified)
- Register visit in the eCRF
- Ensure subject has a rescue inhaler

- Dispense IP
- Collect post-dose PK sample at 2.5 hours post-dose
- Complete eCRF

Other visits when these procedures are part of the visit:

- Have the subject complete questionnaires
- Vital signs
- ECG
- FeNO
- EBC analysis (only at select sites that are properly trained and qualified)
- Spirometry (pre-bronchodilator only)
- Collect lab samples and predose pharmacokinetic sample
- Sputum induction (only at select sites that are properly trained and qualified)

8.1. Efficacy Assessments

8.1.1. Asthma Worsening (Primary Endpoint)

At each visit, the Investigator or designee will:

- Download and review the eDiary report for alerts for AM PEF, rescue medication use, and asthma symptoms
- Have the subject complete the ACQ-5 in clinic and review to assess for an increase in ACQ-5 score ≥ 0.5 compared to baseline
- Measure spirometry at each visit except Visit 3 (Week 2), and the FEV_1 will be assessed to look for a decrease of > 20% from baseline
- Interview the subject to inquire about recent use of systemic corticosteroids (for 3 or more days) for asthma, or an Emergency Department visit or hospitalization for asthma. If the criteria for a severe asthma exacerbation are met, the site staff will complete the exacerbation page within the eCRF. Courses of systemic corticosteroids separated by 7 or more days will be counted as separate severe exacerbations.

8.1.2. eDiary Asthma Parameters and Alerts

The subject will be asked to record the following parameters daily in the eDiary from the Screening visit through the Follow-up visit:

- Morning peak flow (best of three efforts) before rescue medication usage (L/min)
- Puffs of rescue medication used over the previous 24 hours
- Asthma symptom score over the previous 24-hours using a 6-point scale (Appendix 7 in Section 10.7)

- Frequency of awakening due to asthma symptoms requiring rescue medication use

The eDiary is programmed to alert the subject about potential asthma worsening. Please refer to Section 4.1.1 for alert criteria.

Subjects will be issued a paper worksheet to record new medical problems and medications taken during the study. This will be used to assist subject recall in discussions with the Investigator or designee.

The eDiary information is to be downloaded and reviewed at each visit for potential asthma worsening, asthma exacerbations, and to assess compliance with eDiary completion. The subject diary data should be archived by site at the end of the study.

8.1.3. Pulmonary Function Testing including Reversibility

Pre-albuterol/salbutamol morning FEV_1 will be measured using electronic spirometry between 5:00 AM and 12:00 noon and within ± 1 hour from the time of the Screening visit FEV_1 measurement time. Spirometry will be measured at all visits except Visit 3. Subjects should withhold short-acting beta-agonist (SABA) use for ≥ 6 hours prior to measurement of spirometry, long-acting beta-agonists (LABAs) for ≥ 12 hours prior to spirometry and ultra-LABA (eg, vilantrol) > 24 hours prior to spirometry. Additionally, forced vital capacity (FVC), FEV_1/FVC, PEF and forced expiratory flow at 25% to 75% (FEF_{25-75}) will be recorded. For predicted values, the Global Lung Initiative will be used. Additional details for pulmonary function testing will be available in the Study Reference Manual.

Reversibility

At the Screening visit, reversibility in FEV_1 will be measured before and within 30 minutes (± 15 minutes) of albuterol/salbutamol 360/400 µg via metered dose inhaler (MDI) or one nebulized treatment of albuterol/salbutamol. The subject must improve by at least 12% in FEV_1 to be eligible to enter the Run-in period. If the target is not met, historical documentation of reversibility in the 24 months prior to Screening visit or historical documentation of airway hypersensitivity may be allowed upon review and approval by the Medical Monitor.

Reversibility in FEV_1 will also be assessed at Visit 9 (Week 24) or the Early Discontinuation of IP visit.

8.1.4. Asthma Control Questionnaire-5

The ACQ-5 is a five-item questionnaire which has been developed as a measure of the subject's asthma control that can be quickly and easily completed (Juniper, 2005). The questions are designed to be self-completed by the subject. The five questions enquire about the frequency and/or severity of symptoms in the prior week (nocturnal awakening, activity limitation, shortness of breath, wheeze). The response options for each of these questions consists of a zero (no impairment/limitation) to 6 (total impairment/limitation) scale. The minimal clinically important difference (MCID) is 0.5 points.

The subject should be provided with a quiet area in which to complete the questionnaire within the eDiary. The Investigator or designee should ask the subject to complete the questions as accurately as possible. If the subject requests assistance or clarification for any of the questions, he/she will be asked to reread the instructions and to select the answer that best reflects how

he/she felt over the prior week. The subject should be assured that there are no right or wrong answers. The Investigator should not provide the subject with any answer or attempt to interpret any portion of a question.

It is recommended that the ACQ be administered at the same time during each visit. To avoid biasing responses, the subject should not be told the results of diagnostic tests prior to completing the ACQ and the ACQ should be performed prior to any procedures that might influence the subject's responses. Adequate time should be allowed to complete all items on the ACQ.

8.1.5. Asthma Quality of Life Questionnaire- Standardized (AQLQ-S)

The AQLQ-S is a disease-specific, self-administered quality of life questionnaire developed to evaluate the impact of asthma on the subject's quality of life (Juniper, 1993). The questionnaire contains 32 items in 4 domains with a 2-week recall period: activity limitation (11 items), symptoms (12 items), emotional function (five items) and environmental stimuli (4 items). Additionally, each of the 32 responses are averaged to produce an overall quality of life score. Responses are scored on a seven-point scale with a value of 1 indicating total impairment and 7 indicating no impairment. The minimal clinically important difference (MCID) is 0.5 points (Juniper, 1994).

The AQLQ-S will be completed at the visits specified in the SoA (Section 1.3). The AQLQ-S should be completed at approximately the same time during each visit. Subjects should not be told the results of any assessments or study procedures before the questionnaire is completed to avoid biasing the results.

Subjects should complete all questions within the AQLQ-S as accurately as possible. If the subject requests assistance or clarification for completing the question responses, he/she will be asked to reread the question and instructions and encouraged to give the answer that best reflects their current feeling. The subject should be reassured that there are no right or wrong answers.

8.1.6. Sino-Nasal Outcome Test

Sino-Nasal Outcome Test (SNOT-22) is a quality of life instrument to assess the impact of chronic rhinosinusitis and utilizes a 2-week recall period (Hopkins, 2009). The questionnaire will only be completed by subjects with a prior history of sinusitis, nasal polyps, or allergic rhinitis to assess whether GB001 has an impact on this common comorbidity in patients with asthma.

The questionnaire consists of 22 items across 5 domains: Nasal, Ear, Sleep, General and Practical, and emotional. A scale ranging from 0 (no problem) to 5 (problem as bad as it can be) is used to respond to each item in the questionnaire with the total global score ranging from 0 to 110. The global MCID is 8.9.

8.1.7. Hair Assessment

The DP_2 pathway has been implicated as being involved in androgenic alopecia and antagonizing this pathway has shown benefit as a potential treatment for alopecia (Garza, 2012; Nieves, 2014). Therefore, subjects will be assessed for the presence or absence of scalp hair loss at baseline and at conclusion of IP treatment.

A visual scale (Norwood classification for male subjects and Savin classification for female subjects) to characterize the degree of scalp hair loss at baseline and at the end of the study will be used (Gupta, 2016). This information will be complemented with a modified questionnaire to assess patient perceptions of scalp hair growth at the end of the study (Appendix 10; Section 10.11). This questionnaire includes 2 simple questions to describe possible scalp hair growth changes during the study period.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination including but not limited to an evaluation of the lungs and cardiovascular systems as well as visualization of nose for polyps will be conducted as designated in the SoA (see Section 1.3). The presence or absence of hair loss will also be assessed. The results of the physical examination will be recorded in the subject's notes and any significant unfavorable change from the screening exam will be recorded as an AE both in the subject's notes and in the eCRF.
- Height and weight will also be measured and recorded.
- The physical exam should be conducted prior to spirometry.

8.2.2. Vital Signs

- Pulse 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.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be measured after 5 minutes rest and prior to spirometry and ECG measurements.

8.2.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.1 for QTc stopping criteria.
- ECG will be centrally read by the Sponsor's designee via the electronic portal.
- Subjects with evidence of a significant abnormality in the 12-lead ECG obtained at screening, including prolongation of the QTc interval will not be eligible to randomize into the study.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. Details for collection, processing and shipping of samples to the central laboratory are provided in a separate Laboratory Manual.
- The Investigator must review the laboratory report, document this review, and 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor. For additional liver safety monitoring, refer to Appendix 6 (Section 10.6).
  - 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 (Section 10.2), must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3. Adverse Events, Serious Adverse Events, and Adverse Events of Interest

The definitions of an AE, SAE, and AE of Interest can be found in Appendix 3 (Section 10.3).

AE 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, SAE, or AE of Interest.

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

All AEs/SAEs will be collected from the time of signing the ICF until 4 weeks after the last IP dose. For subjects who permanently discontinue IP early but remain in the study, AEs will continue to be collected until the completion of Visit 9 (Week 24) or 4 weeks after the last dose of IP, whichever occurs later.

Medical occurrences that begin before the start of IP but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF 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 (Section 10.3.5). 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 that start 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 (Section 10.3).

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 and liver events will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report from the Sponsor describing a SAE or other specific safety information (eg, summary or listing of SAEs) will review and then file it along with the Investigator's Brochure. The Investigator will then notify the IRB/IEC, if appropriate according to local requirements.

8.3.4. Pregnancy

- Details of all pregnancies in female subjects will be collected as outlined in Appendix 4 (Section 10.4).
- 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 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5. Death Events

All death events will require completion of a specific death data collection page within the eCRF.

Timelines for reporting of death events are identical to the requirements for SAE reporting. (Section 10.3.5).

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

Asthma worsening is the primary efficacy endpoint and is a disease-related outcome not qualifying as an AE unless the Investigator considers asthma worsening to have met the definition of an SAE (Appendix 3; Section 10.3.2). Asthma worsening meeting the definition of an SAE will be reported in the appropriate eCRF (Appendix 3; Section 10.3.5). Asthma worsening not meeting the definition of an SAE should not be reported as an AE. Asthma worsening, as assessed by the primary efficacy endpoint and by the occurrence of SAEs, will be monitored by both the Sponsor and the IDMC on a routine basis.

[redacted]

8.4. Treatment of Overdose

For this study, any dose of IP greater than the prescribed daily dose 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:

1. Contact the Medical Monitor as soon as possible.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.5. Pharmacokinetics

- Blood samples of approximately 6 mL will be collected for measurement of plasma concentrations of GB001 and possibly metabolites of GB001 as specified in the SoA (see Section 1.3):
  - At the Randomization visit, the PK samples will be collected predose and approximately 2.5 hours postdose.
  - For all other visits where PK samples are collected, the sample will be collected at any time during the visit. The subject will be instructed to take their dose in the evening at their regular dosing time and to record the time of dosing on a paper worksheet.
- Each plasma sample will be divided into 3 aliquots.

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

8.6. Pharmacodynamics and Biomarkers

Blood, nasal, and urine samples will be collected at the designated times specified in the SoA (see Section 1.3) and may be used as the basis for multiple exploratory assays to evaluate the effect of GB001 on a range of potential target engagement and PD biomarkers.

Airway samples (eg, nasosorption, sputum, EBC) may be collected at the designated times specified in the SoA at properly trained and qualified sites. These samples may be used for multiple exploratory assays to evaluate the effect of GB001 on potential target engagement and PD biomarkers.

Samples may be stored at a facility selected by the Sponsor, to enable further analysis of biomarker responses to GB001, for a maximum of 8 years (or according to local regulations) following the last subject's last visit for the study.

Residual blood, airway and urine samples may be stored for potential future identification of factors or profiles that correlate with measures of response to GB001.

For more details on the procedures, please refer to the study specific Laboratory Manual.

8.6.1. Induced Sputum

Induced sputum may be collected at selected trained and qualified sites in a subset of subjects with baseline ≥ 2%) with a goal of achieving approximately 20 subjects per treatment group and

15 subjects completing both visits. At randomization and Visit 9 (Week 24) sputum induction may be performed after the protocol required pulmonary function tests have been completed. If the sputum sample collected at randomization is < 2% eosinophils, the Week 24 sample will not be collected.

The process for sputum induction entails having the subject inhale a hypertonic 3% saline solution via a nebulizer. If tolerated, the nebulization is repeated up to 2 additional times using 4% and subsequently 5% saline. The inducted sputum will be processed at the site within 2 hours following completion of the sample collection. The prepared samples will be sent to a specialty lab for analysis. For more details of the methodology, sample preparation, and sample shipping, please refer to the Laboratory Manual.

8.6.2. Fractional Exhaled Nitric Oxide

FeNO may be measured at the visits specified in the SoA utilizing equipment provided by a central vendor. Measurement of FeNO should occur prior to spirometry being conducted. For more details, please refer to the Study Reference Manual.

8.6.3. RNA Transcriptome Research

Transcriptome studies may be conducted using capillary electrophoresis, microarray, and/or alternative equivalent technologies, which facilitates the measurement of the relative abundances of thousands of ribonucleic acid (RNA) species resulting in a transcriptome profile for each blood sample. This would enable the evaluation of changes in the Th2 signature that may correlate with biological response relating to asthma or the action of GB001.

The same samples may also be used to confirm findings by application of alternative technologies. Samples are intended to be collected from all subjects, but may not all be analyzed.

A finger-stick kit may be used at the site and for at-home assessments by the subjects. If used for at-home assessments, the kit will be dispensed at Visit 8 (Week 20). Subjects will be required to conduct the test at home on the same day as Visit 9 (Week 24) and to return the kit as directed.

[redacted]

8.6.5. Blood Biomarker Analyses

A blood biomarker sample may be obtained at baseline and longitudinally to potentially analyze, eg,:

Flow Cytometry: DP_2 expression on lymphocytes and/or granulocytes, an extended CRTH2 phenotyping panel, Th1/Th2/Th17 cell characterization, enumeration of T, B, and/or NK cells

Epigenetic Cell Counting: Number of cells positive for Th1, Th2, and/or DP2 markers; eosinophils, basophils, etc.

[redacted]

8.6.7. Exhaled Breath Condensate Assessment

EBC analysis may be conducted at a subset of sites that are properly trained and qualified.

Non-invasive EBC analysis has shown that leukotrienes, prostaglandins, isoprostane, nitrates, and nitrites can be measured, which are linked to asthma, and may reflect the inflammatory state of the lower airway (Lacombe, 2018; Maniscalco, 2018; Uchida, 2018).

The purpose of this study is to analyze the metabolic signature of volatile organic compounds (VOC) in asthma patients treated with or without GB001 using chromatography/mass spectrometry. The Sponsor hypothesizes that this analysis can identify markers that can potentially be used to measure changes in the airway that predict (at baseline or shortly after the start of treatment) clinical efficacy and are correlated with clinical endpoints, such as exacerbation rate, FEV_1, PEF, etc. This platform may also measure the levels of GB001 in the airway, which may also be correlated with clinical endpoints.

[redacted]

8.7. Genetics

Genetic analyses for possible exploratory pharmacogenetic analysis may be performed on samples from subjects who have consented for this assessment. Subject confidentiality will be maintained.

Samples will be collected from subjects, who have consented to participate in the genetic analysis component of the study, where permitted by law and local authorities. Participation is a subject-level decision, and those subjects who do not wish to participate in the genetic research may still participate in the study.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This study is designed to demonstrate the superiority of GB001 versus placebo, when added to SOC therapy, on the primary endpoint of the proportion of subjects who experience worsening of asthma by Week 24.

9.2. Sample Size Determination

A total sample size of approximately 480 subjects (approximately 120 per treatment group, randomized in a 1:1:1:1 ratio) is estimated to provide 80% power to detect a reduction in odds of 66% between each GB001 group and placebo at an 0.050 two-sided level of significance for the primary endpoint of the proportion of subjects who experience worsening of asthma by Week 24. This assumes the proportion of subjects who experience worsening of asthma by Week 24 is 25% in the placebo group and 10.2% in each GB001 group and a dropout rate of 8%.

Randomization will be stratified by baseline ICS dose (medium or high, as defined in Appendix 9; Section 10.9) and country.

9.3. Populations for Analyses

The following major analysis populations are defined:

- All enrolled population: All subjects who consent to study participation. This population will be utilized for summaries of subject disposition.
- Run-in period population: All enrolled subjects who enter the Run-in period. This population will be utilized for summaries of subject disposition.
- 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.
- Per-protocol (PP) population: All subjects in the ITT population who do not violate terms of the protocol that may affect primary or secondary efficacy outcomes. The criteria for the PP population will be determined prior to unblinding and will be described in detail in the Statistical Analysis Plan (SAP).
- Safety population: All subjects who receive at least 1 dose of IP, with subjects grouped according to their actual treatment.

9.4. Statistical Analyses

In general, continuous variables will be summarized using the number of subjects with non-missing data, mean, standard deviation, minimum, and maximum. Continuous variable summaries will include standard error, where appropriate. Categorical variables will be summarized using counts and percentages. Baseline value will be defined as the last non-missing value on or before the date of the first dose of IP. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

The ITT Population will be utilized for efficacy analyses.

9.4.1.1. Primary Efficacy Analysis

For the primary endpoint of the proportion of subjects who experience worsening of asthma by Week 24, logistic regression modeling will be used to compare each GB001 group with placebo. The model will include factors for treatment group, baseline ICS dose (medium or high), region (pooled country), baseline FEV_1, and baseline ACQ-5. Odds ratios (ORs), p-values, and corresponding 95% confidence intervals (CIs), along with the absolute differences and corresponding 95% CIs, will be summarized for each GB001 group versus placebo.

A subject who prematurely withdraws from the study without experiencing asthma worsening will be assigned asthma worsening status by Week 24 (yes/no) based on their IP discontinuation and study withdrawal reasons. If a subject's reason for IP discontinuation or study withdrawal is indicative of lack of efficacy or is an AE indicative of asthma worsening, a determination will be made prior to study unblinding regarding whether the subject should be considered to have had asthma worsening for the primary endpoint. Otherwise, subjects who prematurely withdraw from the study will be considered to have not experienced asthma worsening for the primary endpoint. Details of handling of missing data for the primary endpoint will be fully described in the SAP.

9.4.1.2. Secondary Efficacy Analysis

The secondary endpoints of change from baseline in ACQ-5 score, change from baseline in morning pre- and post- bronchodilator FEV_1, and change from baseline in morning PEF to Week 24 will be analyzed using analysis of covariance (ANCOVA) models. Differences in least-squares means, along with p-values and two-sided 95% CIs, for each GB001 group versus placebo will be constructed from the ANCOVA models.

Time to asthma worsening will be compared between treatment groups using a Cox proportional hazards model. Covariate adjustment will be the same as for the primary endpoint. Kaplan-Meier summaries of the proportion of subjects with asthma worsening over time will also be presented.

The annualized rate of severe asthma exacerbations will be analyzed using a negative binomial regression model, with the total number of severe exacerbations as the outcome and the logarithmic transformation of follow-up time as the offset parameter. Rate ratios, along with p-values and two-sided 95% CIs, for each GB001 group versus placebo will be constructed from the negative binomial regression model. If the distribution of severe exacerbation data is under-dispersed, or if the negative binomial regression model fails to converge, a Poisson regression model will be used instead of the negative binomial regression model. Exacerbations for which the courses of systemic corticosteroids are separated by 7 or more days will be counted as separate events.

[redacted]

9.4.2. Safety Analyses

All safety analyses will be performed using the Safety Population.

Safety analyses will be focused on treatment-emergent adverse events, defined as an AE with onset on or after the start of study treatment. The incidence of AEs and SAEs will be summarized by treatment group, including the incidence by system organ class and preferred term.

Laboratory, vital signs, and ECG data will be analyzed using summary statistics for continuous parameters. The number and frequency of subjects with pre-defined abnormalities considered clinically significant will be presented. For laboratory parameters, the number and frequency of subjects with shifts from baseline to low, normal, or high values will also be presented.

9.4.3. Other Analyses

Tertiary and exploratory endpoints, including PK, PD, and biomarker exploratory analyses, may be described in a separate SAP. The population PK analysis and PD and biomarker analyses may be presented separately from the main clinical study report (CSR).

9.5. Interim Analyses

An unblinded interim analysis will be conducted after the first 320 subjects have completed the study or have prematurely withdrawn from the study. The purpose of this interim analysis is to inform further development of GB001. The interim analysis will consist of a comprehensive assessment of GB001's benefit-risk profile, including, but not limited to, evaluation of primary and secondary efficacy endpoints and safety outcomes.

The interim analysis will be performed and reviewed by select unblinded Sponsor (or designee) personnel who will not be directly involved in the conduct of the study following the interim analysis and the IDMC. Subjects, Investigators and other site personnel, and Sponsor (or designee) personnel who remain directly involved in the conduct of the study following the interim analysis will remain blinded to treatment assignment throughout, until after the completion of the study. Details of the select unblinded Sponsor (or designee) personnel and measures to ensure rigorous maintenance of the blind will be provided prior to unblinding as part of an interim statistical analysis plan.

Given that the interim analysis is administrative, will not result in any statistical inferences being made, and is not intended to result in any modification to the study (ie, the study will be continued and completed regardless of the interim analysis results), no Type I error will be allocated to the interim analysis.

9.5.1. Independent Data Monitoring Committee

An IDMC will regularly monitor overall safety and emerging efficacy results, as well as general aspects of study conduct, to ensure that the benefits and risks of study participation remain acceptable. Following an initial organizational IDMC meeting, the first IDMC meeting at which results are reviewed will occur after approximately 50 subjects have been randomized and have completed 12 weeks on study or within 12 months of the first subject randomized.

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

Meeting structure, schedule, and procedures, including communication between the Sponsor and the IDMC, the content and format of IDMC reports, and other relevant details, will be determined in consultation with IDMC members and detailed in a separate IDMC charter.

10. APPENDICES

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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, Investigator Brochure, eDiary 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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. 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 entered 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. Subjects 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. Subjects who decline to participate in this optional research will not provide this separate signature.
- A pharmacogenetics (PGx) consent form must be offered to all subjects and the process must be documented, unless prohibited by local regulations.

10.1.3. 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.

10.1.4. 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.
- Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

10.1.5. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic 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 physically or 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.

10.1.6. 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.

10.1.7. 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

10.1.8. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 2 and Table 3 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.

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 in subject's source records.

Table 2: Protocol-Required Safety Laboratory Assessments

Hematology	
White blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Red blood cell (RBC) with indices (MCV and MCH)
Hemoglobin	Hematocrit
Platelet count	
Clinical Chemistry	
Alanine aminotransferase (ALT)	Aspartate aminotransferase (AST)
Alkaline phosphatase[1]	Gamma-glutamyl transferase (GGT)
Total and direct bilirubin (fractionated)	Albumin
Calcium	Blood urea nitrogen (BUN)
Sodium	Creatinine
Chloride	Potassium
Glucose (non-fasting)	Lactic dehydrogenase (LDH)
Uric acid	Magnesium
Total protein	Total bile acid
Coagulation	
INR	
Urinalysis	
Basic urinalysis (dipstick) to be performed at the Screening visit, Week 24, and Early Discontinuation of IP/Withdrawal from Study visits. Reflex microscopic evaluation will be performed if the dipstick is abnormal.	

Other Laboratory Assessments
• Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Viral hepatitis serology (hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Urine cotinine

[1] Fractionation of ALP if ALP > 1xULN.

The additional tests listed in Table 3 will be collected only as part of liver safety actions and follow up. See also Appendix 6 (Section 10.6).

Table 3: Liver Safety Laboratory Assessments

Hematology
Expanded viral hepatitis serology: • Hepatitis A immunoglobulin M (IgM) antibody • HBsAg and HBcAb • hepatitis C RNA • cytomegalovirus IgM antibody • Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) • hepatitis E IgM antibody • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, quantitative total immunoglobulin G (IgG) or gamma globulins, and serum acetaminophen
Chemistry
• Bile acids (bile acid, fractionated and total, liquid chromatography-tandem mass spectrometry (LC/MS-MS) if bile acid > 3 x ULN) • International normalized ratio (INR) • Serum creatine phosphokinase (CPK) • Lactate dehydrogenase (LDH)

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of IP, 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 other than the disease under study 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 AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • 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.

10.3.2. 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:
a. Results in death
b. 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.
c. 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.
d. 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.
e. Is a congenital anomaly/birth defect

An SAE is defined as any untoward medical occurrence that, at any dose:
f. 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.

10.3.3. Adverse Events of Interest

Liver disorder is considered a potential risk and will be closely monitored. As such, liver events have been deemed of interest in the GB001 program.

Adverse events of interest will include alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased and/or associated preferred terms alone or associated with other conditions of concern, that result in temporary or permanent discontinuation of IP as defined in Appendix 6 (Section 10.6, Table 5) with the exception of events for which subjects cannot be monitored. Follow-up liver laboratory values (Table 3, Appendix 2 [Section 10.2]) and additional information to characterize the etiology of the event are mandatory and specified in Appendix 6 (Section 10.6).

10.3.4. Recording and Follow Up of Adverse Events and Serious Adverse Events

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/AE of Interest 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 Investigator's Brochure (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 post-mortem 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.

10.3.5. 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 Medical Monitor 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 Medical Monitor and submitting the paper SAE report form via the contacts below.
- Contacts for SAE reporting can be found in below.

[redacted] Non-North America: Use numbers and access codes specific to the country as provided by Sponsor.	Or if not available, [redacted]

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman 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 1 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 the site personnel's 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.
   - Females 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 study enrollment.

Contraception Guidance

Female Subjects:

- 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 (see table below), at least 1 month prior to Screening, during the intervention period, and for 28 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 (urine or serum as required by local regulations) within 24 hours before the first dose of IP.
  - If a urine test 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.

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

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 o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] o oral o 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.)*

[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] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, 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).

Collection of Pregnancy Information

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. The subject will be followed until birth or termination of pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- 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 Section 10.3.5. 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.

10.5. Appendix 5: Genetics

Use and Analysis of DNA

- Genetic 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 will be collected for DNA analysis from consenting subjects.
- Samples may be used for research related to GB001 and/or asthma and related diseases. They may also be used to develop tests/assays including diagnostic tests related to GB001 and DP2 inhibitors and atopic disease. Genetic research may consist of the analysis of prespecified candidate polymorphisms.
- Samples may be analyzed for variation in candidate genes which dramatically affect the pharmacokinetics of GB001, 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 cytochrome P450 enzymes (eg, CYP2D6). The effects of single nucleotide polymorphisms on the PK of GB001 uncovered in the course of this study may help guide future clinical studies and regulatory review of GB001. 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 efficacy observations during the life of the study.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GB001 of this class to understand study disease or related atopic conditions.
- The results of genetic analyses may be reported in the CSR or 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 GB001 continues but no longer than 8 years or other period as per local requirements.

The following genetic parameters may be evaluated in this study:

- Genetics (DNA):

  SNPs in a) drug metabolizing and enzymes, b) DP_2 pathway genes, c) asthma & atopic pathway genes, e.g. vitamin D

10.6. Appendix 6: Liver Safety - Actions and Follow-up Assessments

Liver chemistry will be evaluated as specified in the SoA (Section 1.3) and Appendix 2 (Section 10.2). Parameters will include ALT, AST, GGT, bilirubin, total bile acids, and ALP.

For subjects with ALT or AST > 1 × ULN and < 3 × ULN or total bilirubin or direct bilirubin > 1 × ULN and ≤ 1.5 × ULN, confirm the value within 24 to 48 hours. Contact the Medical Monitor to determine the appropriate liver monitoring schedule (eg, weekly or twice a week).

The criteria requiring additional liver monitoring with possible interruption of study intervention are detailed in Table 4.

Table 4: Liver Chemistry Criteria Requiring Additional Monitoring with Possible Interruption of Investigational Product

Criterion	Actions
ALT or AST ≥ 3 × ULN and < 5 × ULN **or** total bilirubin or direct bilirubin > 1.5 × ULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks	• Notify the Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety. "Additional Liver Panel" in Table 5 may be requested by the Medical Monitor • Confirm values within 24 to 48 hours via repeat labs. If unable to obtain repeat labs within 48 hours, discontinue IP. • Decision to continue or interrupt study intervention will be determined by the Investigator and the Medical Monitor • Subject must return weekly or more frequently for repeat liver chemistry tests (ALT, AST, GGT, ALP, total bile acids, and bilirubin) until the abnormalities resolve, stabilize or return to baseline. • If at any time the subject meets liver chemistry interruption criteria (as specified in Table 5), then follow the instructions in "Actions and Follow-up Assessments" in Table 5 and in consultation with the Medical Monitor initiate relevant assessment procedures

In the case of AEs of interest (Section 10.3.3), potential re-challenge will be restricted to potential DILI cases that have been assessed as unlikely or not related to IP by the HAC and after liver enzymes have returned to baseline levels. When re-challenging with IP, obtain repeat liver chemistries twice weekly in the first 2 weeks and then weekly for 6 weeks after the re-challenge. If there is a rise in liver enzymes > 2 × ULN, then IP should be discontinued permanently.The criteria requiring interruption of IP with additional liver monitoring is detailed in Table 5.

Table 5: Liver Chemistry Criteria Requiring Investigational Product Interruption and Additional Monitoring

Liver Chemistry – IP Interruption Criteria	
ALT/AST (single occurrence)	ALT or AST ≥ 5x ULN
ALT/AST	ALT or AST ≥ 3x ULN persists for ≥ 4 weeks
+ Bilirubin [a,b]	ALT or AST ≥ 3x ULN **and** bilirubin > 2x ULN (> 35% direct bilirubin)
+ INR [b]	ALT or AST ≥ 3x ULN **and** international normalized ratio (INR) > 1.5, if INR measured
+ Cannot Monitor	ALT or AST ≥ 3x ULN **and** cannot be monitored weekly for 4 weeks
+ Symptomatic [c]	ALT or AST ≥ 3x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue IP • Report the event to the Medical Monitor **within 24 hours** • Complete the liver event eCRF and complete an SAE data collection tool if the event also met the criteria for an SAE[b] • Perform liver chemistry follow-up assessments • Monitor the subject until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) • **Do not restart/rechallenge** subject with IP unless Medical Monitor approval is granted • If restart/rechallenge **not granted**, permanently discontinue IP and continue subject in the study for any protocol specified follow up assessments **MONITORING:** • Repeat liver chemistry tests (include ALT, AST, GGT, alkaline phosphatase, total bile acids, bilirubin, and INR) and perform liver event follow-up assessments within **24 hours** • Monitor subject twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended	**Additional Liver Panel** • Viral hepatitis serology [d] • Obtain INR and recheck with each liver chemistry assessment until the ALT and/or AST values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • Fractionate bilirubin, if total bilirubin > 2x ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the adverse event (AE) report form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF • Record alcohol use on the liver event alcohol intake eCRF • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen assay • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease

[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 ≥ 3x ULN **and** bilirubin > 2x 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 ≥ 3x ULN **and** bilirubin > 2x ULN (> 35% direct bilirubin) or ALT or AST ≥ 3x 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).

[d] Includes: expanded viral hepatitis serology (Table 3).

10.7. Appendix 7: Daily Asthma Symptom Score

Each morning subjects will record in the eDiary an assessment of the severity of their asthma symptoms during the prior 24 hours using the following scale:

- 0 = No symptoms
- 1 = Symptoms for one short period
- 2 = Symptoms for two or more short periods
- 3 = Symptoms for most of the prior 24 hours which did not affect my ability to carry out my daily activities
- 4 = Symptoms for most of the prior 24 hours which did affect my ability to carry out my daily activities
- 5 = Symptoms so severe that I could not go to work/school or complete my normal daily activities

10.8. Appendix 8: Prohibited Medications and Treatments

Bronchial thermoplasty and radiotherapy are excluded in the 12 months prior to Screening visit and throughout the study. Continuous positive airway pressure, oxygen therapy, or allergen immunotherapy may not be initiated after the Screening visit.

The following medications must be washed out for the period noted in the table below and prohibited throughout the study as they may interfere with endpoint interpretation.

Medication	**Washout time prior to Screening visit**
mepolizumab, reslizumab, benralizumab, omalizumab, dupilumab	5 half-lives (~4 months)
Immunosuppressive medications such as those listed below (not all inclusive)	
regular use of oral corticosteroid	1 month
intramuscular long-acting depot if used to treat a condition other than asthma	3 months
methotrexate, azathioprine, imatinib, sulfasalazine, cyclosporine	1 month
chemotherapy used for conditions other than asthma	6 months

GB001 is metabolized at least in part by CYP3A4, hence the need to restrict the usage of known CYP3A4 inducers and inhibitors. Thus, the following is a non-exhaustive list of medications and drink/food which may inhibit or induce CYP3A4 activities that will be prohibited 14 days prior to randomization through the Safety Follow-up visit:

Prohibited Food/Drink (list is not all inclusive)	**Washout time prior to Randomization**
Grapefruit or grapefruit juice	14 days
Seville Oranges	
Marmalade	
Moderate or Strong Inhibitors of CYP3A4 (list is not all inclusive)	**Washout time prior to Randomization**
ciprofloxacin	14 days
erythromycin, clarithromycin, telithromycin	
fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole, oral clotrimazole	
Diltiazem	
aprepitant	
verapamil	
nefazodone	
curcumin	
Moderate or Strong Inducers of CYP3A4 (list is not all inclusive)	**Washout time prior to Randomization**
carbamazepine	14 days
phenytoin	
rifampin	
modafinil	
St. John's wort	

A more comprehensive but still non-exhaustive list of prohibited medications and drinks/food to prevent potential metabolic drug-drug interactions will be provided in a manual to study sites.

10.9. Appendix 9: Restricted Medications and Treatments

Restricted medications are defined as medications which should be avoided, if possible; however, they are not prohibited during this study if stable for at least one month before screening. If such medications are required, consider switching to another medication in the class that is not restricted.

Medications known to be associated with drug-induced liver injury	
Allopurinol	Interferon beta
Amiodarone	Isoniazid
Amoxicillin-clavulanate	Methyldopa
Anabolic steroids	Minocycline
Atorvastatin	Nevirapine
Carbamazepine	Nimesulide
Chlorpromazine	Nitrofurantoin
Oral contraceptives	Propylthiouracil
Dantrolene	Quinidine
Diclofenac	Pyrazinamide
Didanosine	Simvastatin
Disulfiram	Sulfamethoxazole/Trimethoprim
Flucloxacillin	Sulfonamides
Halothane	Sulindac
Hydralazine	Telithromycin
Ibuprofen	Ticlopidine
Interferon alpha/Peginterferon	Valproate

Source: Björnsson, 2016.

10.10. Appendix 10: Estimated Clinical Comparability of Medium and High Doses of Inhaled Corticosteroids

Medication	Medium Dose mcg/day	High Dose mcg/day
Beclomethasone dipropionate CFC	>500-1000	>1000
Beclomethasone dipropionate HFA	≥200-399	≥400 [a]/320 [b]
Beclomethasone extra-fine/LABA combination	≥200-399	≥ 400
Budesonide DPI	>400-800 [a]/>320--400 [b]	>800 [a]/640 [b]
Budesonide/LABA combination	**Ex-United States:** ≥400-800 [a]/≥320-640 [b]	**Ex-United States:** >800 [a]/640 [b]
	United States: 320 -639 [b]	**United States:** ≥ 640 [b]
Ciclesonide	>160-320	>320
Fluticasone furoate/LABA DPI	92 [c]/100	184 [c]/200
Fluticasone propionate/formoterol MDI	>230-460 [b]/250-500 [a]	>460 [b]/500 [a]
Fluticasone propionate DPI	>250-500	>500
Fluticasone propionate/LABA HFA	>230-460 [b]/250-500 [a]	>460 [b]/500 [a]
Fluticasone propionate/LABA DPI	>250-500 /233-465 [c]	> 500 /465 [c]
Mometasone furoate	>220-440 />200-400 [c]	>440 /400 [c]
Mometasone furoate/LABA	200-400 [c]	>400 [c]
Triamcinolone acetonide	>1000-2000	>2000

Abbreviations: CFC, chlorofluorocarbon propellant; DPI, dry powder inhaler; HFA, hydrofluoroalkane propellant; ICS, inhaled corticosteroid; NA, not applicable

[a] ex-valve

[b] ex-actuator

[c] dose delivered

10.11. Appendix 11: Assessment of Hair Loss

Questionnaire to Assess Patient Perceptions of Hair Growth

1. Do you lose hair to the point that this is concerning? ☐ Yes ☐ No
2. Do you have any bald spots? ☐ Yes ☐ No

Note: If the subject answered "Yes" to any of the questions above, the site will complete the graphical visual assessment for male and female subjects (Norwood and Savin Scales), respectively.

In those subjects who completed the above information, **at the end of the study** (Last IP Visit) the following questions should be completed, please check only one box:

a. Since initiation of the study, I noticed my bald spot is getting smaller:

Strongly agree	
Agree	
A little better	
The same	
A little worse	
Somewhat worse	
A lot worse	

b. Overall, since initiation of the study, I noticed that the growth of my hair is:

Greatly increased	
Moderately increased	
Slightly increased	
The same	
Slightly decreased	
Moderately decreased	
Greatly decreased	

10.12. Appendix 12: Guidance to Address a Pandemic or Other Global Health Emergencies and Potential Impact on the Clinical Study

In the occurrence of a global health pandemic 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 (FDA, 2020; EMA, 2020; Health Canada, 2020; MHRA, 2020).

Adjustments to the GB001-2001 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 trial integrity during the COVID-19 pandemic (FDA, 2020; EMA, 2020; Health Canada, 2020; MHRA, 2020). Member states within the National Competent Authorities may issue their own guidance requiring country specific recommendations to be followed.

- In the case of missed visits due to COVID-19 (or other health pandemic) related reasons:
  - The site should make every effort to contact the subject to confirm and document the reason for the missed visit, and at minimum evaluate AEs/SAEs, concomitant medications, and asthma exacerbations in order to assess subject status.
  - The subject should continue to collect the daily AM PEF and eDiary responses on the eDiary. The eDiary will provide an alert to potential asthma worsening, as described in Section 4.1.1. In the event of an alert, the subject should contact the site staff as soon as practical to assess the subject's asthma status.
- Alternative methods of collecting study assessments may be considered where possible:
  - Questionnaires, including ACQ-5, AQLQ, and SNOT-22, may be self-administered by the subject at home.
  - In certain situations, with Sponsor approval, a local laboratory may be used.
- Alternative methods of supplying IP to study subjects (eg, direct-to-patient shipment from site) may be considered where possible.
  - With prior sponsor approval, IP may be supplied via alternative methods provided that laboratory assessments are able to be performed prior to the delivery of IP. In all cases, study subjects must provide consent for alternative delivery methods. Documentation of consent will be captured in the subject's study records.

10.13. Appendix 13: Abbreviations

Abbreviation Term	Description
ACQ	Asthma Control Questionnaire
AE	adverse event
ALT	alanine aminotransferase
AM	morning
ANCOVA	analysis of covariance
AQLQ-S	Asthma Quality of Life Control Questionnaire (standardized)
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CPK	serum creatine phosphokinase
CRTh2	chemoattractant receptor-homologous molecule expressed on Th2
CSR	clinical study report
CTFG	Clinical Trial Facilitation Group
DILI	drug induced liver injury
DP_2	prostaglandin D_2 receptor
DPI	dry powder inhaler
EBC	exhaled breath condensate
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ES	extension study
EW	early withdrawal
FEF_{25-75}	forced expiratory flow at 25% to 75%
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone

Abbreviation Term	Description
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GINA	Global Initiative for Asthma
HAC	Hepatology Assessment Committee
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HPLC	high performance liquid chromatography
HRT	hormonal replacement therapy
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroid
IDMC	Independent Data Monitoring Committee
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	hormone-releasing system
LABA	long-acting beta agonist
LAM	lactational amenorrhoea method
LAMA	long-acting muscarinic antagonist
LDH	lactate dehydrogenase
LTRA	leukotriene receptor antagonist

Abbreviation Term	Description
MCID	minimal clinically important difference
MDI	metered dose inhaler
OR	odds ratio
PD	pharmacodynamic
PEF	peak expiratory flow
PGD_2	prostaglandin D_2
PK	pharmacokinetic
PP	Per-protocol
PRO	patient reported outcomes
QTcF	Fridericia's correction formula for QT interval (interval between Q wave and T wave)
RBC	red blood cell
RNA	ribonucleic acid
SABA	short-acting beta-agonist
SAE	serious adverse event
SAP	Statistical Analysis Plan
SNOT-22	Sino-Nasal Outcome Test
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
Th2	T Helper cell type 2
ULN	upper limit of normal
VOC	volatile organic compounds
WBC	white blood cell
WOCBP	women of childbearing potential

10.14. Appendix 14: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	**Date**
Amendment 3 (v4.0)	18-Feb-2020
Amendment 2 (v3.0)	28-Aug-2019
Amendment 1 (v2.0.0)	28-Feb-2019
Original Protocol (v1.0.0)	02-Aug-2018

Amendment 3 (v4.0; 18 Feb 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to enhance monitoring of liver parameters during the conduct of the trial.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities; Section 1.2 Schema	Addition of a Week 1 visit (Visit 2.5) serum chemistry panel (liver) following Randomization (Visit 2)	Week 1 visit was added to enhance laboratory monitoring during the first month following IP initiation
Section 6.2.5 Unblinded Sponsor Medical Monitor	Added new monitoring guidelines	To enable unblinded medical monitoring of liver and other laboratory parameters of interest by a designated Sponsor Medical Monitor in order to protect subject safety
Section 10.3.3 Adverse Events of Interest	Updated language describing adverse events of interest	Clarified definition of adverse events of interest
Section 10.6 Appendix 6: Liver Safety - Actions and Follow-up Assessments	Modified: • Discussion of possible Investigational Product (IP) continuation or discontinuation if ALT or AST ≥ 3 × ULN or total bilirubin	To enhance monitoring of liver parameters during the conduct of the trial

Section # and Name	Description of Change	Brief Rationale
	or direct bilirubin > 1.5 × ULN and potential triggering of appropriate follow-up to include Liver Safety Laboratory assessments • ALT or AST > 1 × ULN and < 3 × ULN or total bilirubin or direct bilirubin > 1 × ULN and ≤ 1.5 × ULN, confirm the value within 24 to 48 hours	
Global Change	Minor revisions to text.	Administrative clarifications were incorporated, and typographical errors were corrected.

Amendment 2 (v3.0; 28 Aug 2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to enhance monitoring of liver parameters during the conduct of the trial and to provide guidance on drugs that may be associated with hepatoxicity, to provide clarification on eligibility criteria, and to evaluate annualized rate of severe asthma exacerbations as a secondary (rather than exploratory) endpoint.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis; Section 3 Objectives and Endpoints; Section 9.4.1.2 Secondary Efficacy Analysis	Updated annualized rate of severe asthma exacerbations from tertiary/exploratory to secondary endpoint.	Given the clinical importance of the assessment of severe asthma exacerbation, this has been elevated to a secondary endpoint.
Section 1.3 Schedule of Activities	• Notes on total bile acid, international normalized ratio	• Addition of INR measurement at baseline. Collection of

Section # and Name	Description of Change	Brief Rationale
	(INR), and fractionation of ALP if ALP > 1xULN were added. • Added assessment of clinical chemistry at Week 3.	a total bile acid sample at every visit, and fractionation of ALP if ALP > 1xULN. • Week 3 visit was added to enhance laboratory monitoring during the first month following IP initiation.
Section 2.2 Background	Added recent results from post-hoc analyses.	Updated with results which suggest that GB001 favorably influences lung function in subjects with Type 2 markers of inflammation.
Section 2.3.1 GB001 Risk/Benefit Assessment	Revised data for GB001.	Clarified risk/benefit profile.
Section 5.1 Inclusion Criterion #8	Criterion for airway hyperresponsiveness was updated.	Extended period of reversibility and added historical demonstration of airway hyperresponsiveness.
Section 5.2 Exclusion Criteria #4	Added known history of non-alcoholic fatty liver disease (NAFLD) or Gilbert's Syndrome.	Clarified liver-related pre-existing conditions.
Section 5.3 Randomization Criteria #8	Added absolute eosinophil count and white blood cell (WBC) count criteria.	Enhance safety characterization of the study population with eosinophilic asthma.
Section 6.4.2 Restricted Medications; Section 10.9 Appendix 9: Restricted Medications and Treatments	Added to the list of restricted medications those that are known to have potential for liver toxicity.	Increased awareness of medications which may impact liver effects.
Section 9.4.1.2 Secondary Efficacy Analysis	Added statistical analysis methodology for annualized rate of severe asthma exacerbation.	Included statistical analysis methodology given this has been elevated to a secondary endpoint.

Section # and Name	Description of Change	Brief Rationale
Section 10.2 Appendix 2: Clinical Laboratory Tests Table 2	Total bile acid, INR, and fractionation of ALP if ALP > 1xULN were added. Clarified urinalysis.	To enhance monitoring of liver parameters during the conduct of the trial.
Global Change	Minor revisions to text.	Administrative clarifications were incorporated, and typographical errors were corrected.

Amendment 1 (v2.0.0; 28 Feb 2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to provide clarification on Inclusion/Exclusion criteria, incorporate new information based on the GB001-1901 study, and to make administrative protocol clarifications.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities; Section 4.1.1 Study Design	Written informed consent text was updated.	The modification was made to clarify that informed consent may be obtained prior to Visit 1 to allow for medication washouts and obtaining historical medical records when necessary.
Section 1.3 Schedule of Activities	Hepatitis B surface antigen and Hepatitis C antibody text was updated.	Clarification to include indeterminate test result.
	At-home RNA Transcriptome Research text was updated.	Test removed from Early Discontinuation visit due to logistics.
	Nasal sample collection was separately listed.	Clarification to avoid confusion so that all subjects provide sample.
	Notes on sputum eosinophil and neutrophil	Clarification on timing of sputum and exhaled

Section # and Name	Description of Change	Brief Rationale
	and exhaled breath condensate assessments at Randomization visit were added.	breath condensate analysis and first dose.
Section 3 Objectives and Endpoints	The text on pharmacokinetic (PK) analysis was updated. Exploratory endpoint was added.	The minor update clarified that PK samples would be collected from plasma. Exacerbations was added as exploratory endpoint.
Section 4.2.2 Placebo Rationale	Text added on timing of IDMC meeting.	Clarification of timing of IDMC meeting.
Section 5.1 Inclusion Criteria #3; Section 8.3.4 Pregnancy; Section 10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Criterion for male contraception was removed. Data on pregnancies of male partners of female subjects will no longer be collected. Contraceptive guidance for male subjects was removed. Collection of information from male subjects with partners who become pregnant has been removed.	Per CTFG Guidance Section 2.3, no male contraception is required.
Section 5.1 Inclusion Criteria #6	Criteria for ICS plus additional controller was updated.	Clarification on length of prior treatment with medium or high dose ICS and clarification of the use of additional controller medication.
Section 5.1 Inclusion Criteria #7; Section 5.3 Randomization Criteria	The lower limit for FEV1 criterion was removed.	Studies in subjects with severe asthma have been conducted without lower limit of FEV1. Exclusion of subjects with low FEV1 will be based on PI's assessment.
Section 5.1 Inclusion Criteria #8	Text on reversibility was revised.	Clarification on use of equivalent dose of nebulized bronchodilator.
Section 5.2 Exclusion Criteria #1	Text was added to exclude smoking of any substance.	This clarification was made to include marijuana, its

Section # and Name	Description of Change	Brief Rationale
		components, and any other substances which may be smoked.
Section 5.2 Exclusion Criteria #7	Text around ECG assessment was updated.	This modification was made to clarify that ECG assessment could be repeated.
Section 5.2 Exclusion Criteria #18	Text added to clarify criterion.	Clarification on reasons for excluding subjects who may participate in another study.
Section 5.4 Screen or Run-In Failures	Text added to clarify designation of Run-in failure.	Clarification on Run-in failure definition for this study.
Section 6.2.4 Unblinding of an Individual Subject	Text added to clarify conditions for unblinding.	Clarification of procedures to protect samples and data for unblinding.
Section 6.4.2 Rescue Medicine	Text was updated to provide additional details.	This modification was made to clarify use of rescue medication and data capture.
Section 7.1.2 Pregnancy	Removed text on Follow-up visit.	Clarification on procedures if the subject who becomes pregnant.
Section 7.2 Subject Withdrawal from the Study	Updated text to provide further clarity.	Clarification on reasons for subject withdrawal from study.
Section 8 Study Assessments and Procedures	Text was added to description of Screening and Randomization visits.	Clarification on timing of procedures.
Section 8.1.1 Asthma Worsening	Text was added to clarify the timing/duration of exacerbations.	Clarification of the interval between two exacerbations.
Section 8.6.3 RNA Transcriptome Research	Text was updated.	Clarification that not all samples may be analyzed.
Section 8.6.5 Blood Biomarker Analyses	Text was updated.	Simplification and clarification of possible analyses.
Section 9.3 Populations for Analyses	Text added for clarity.	Clarification of populations for analyses.

Section # and Name	Description of Change	Brief Rationale
Section 9.4 Statistical Analyses	Text added for clarity.	Clarification on summaries of variables.
Section 9.4.1 Efficacy Analyses	Subheading was added on efficacy analyses.	Clarification of the population for efficacy analyses.
Section 10.1.2 Informed Consent Process	Text was added to describe pharmacogenetics consent form.	Clarification of the process for collecting PGx informed consent.
Section 10.2 Appendix 2: Clinical Laboratory Tests Table 3; Section 10.6 Appendix 6 Table 5	Specific acetaminophen assay was removed.	Type of acetaminophen assay is no longer specified to allow flexibility in assay performed.
Section 10.3.5 Reporting of SAEs	Contact information and paper submission of SAE report was updated.	Update and clarification of contact information and on paper submission of SAE report.
Section 10.6 Appendix 6: Liver Safety - Actions and Follow-up Assessments	"Not required in China" was removed.	Updated.
Section 10.8 Appendix 8: Prohibited Medications and Treatments	Table was updated.	New data indicated that GB001 is not expected to have clinically significant drug-drug interactions with substrates of CYP2C8, CYP2C9, OATP1B1/1B3, and Pg-p. These data supported change in prohibited medications and treatments.
Section 10.9 Appendix 9: Estimated Clinical Comparability of Medium and High Doses of Inhaled Corticosteroids	Table was updated.	Update due to availability of new products.
Global Change	Minor revisions to text.	Typographical errors were corrected.

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