CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Effect of GB001 in Patients with Chronic Rhinosinusitis with or without Nasal Polyps
Protocol Number:	GB001-2101
Compound Number:	GB001
Study Phase:	Phase 2a
Short Title:	GB001 in Adult Subjects with Chronic Rhinosinusitis
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:	[redacted] [redacted] **EudraCT**: 2019-001682-33
Version:	5.0
Approval Date:	16 April 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

GB001-2101: A Phase 2a, randomized, double-blind, placebo-controlled, multi-center study to evaluate the effect of GB001 in patients with chronic rhinosinusitis with or without nasal polyps

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 of Technical Requirements for Pharmaceuticals for Human Use (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 5 (v5.0)	16 Apr 2020
Amendment 4 (v4.0)	18 Feb 2020
Amendment 3 (v3.0)	28 Aug 2019
Amendment 2 (v2.1)	02 May 2019
Amendment 1 (v2.0.0)	05 Apr 2019
Original Protocol (v1.0.0)	24 Jan 2019

Amendment 5 (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 primary 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 1.3 Schedule of Activities; Section 1.2 Schema; Section 4.1.1 Study Design	Addition of Week 5 (Visit 4.25) and Week 6 visits (Visit 4.5) clinical chemistry panels	Week 5 and 6 visits were added to enhance laboratory monitoring during the first two months following IP initiation
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 re-challenge with investigational product in the case of adverse events of interest
Section 10.11 Appendix 11: 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 compliance with good clinical practice (GCP), and minimizing

Section # and Name	Description of Change	Brief Rationale
		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 2a, randomized, double-blind, placebo-controlled, multi-center study to evaluate the effect of GB001 in patients with chronic rhinosinusitis with or without nasal polyps

Short Title: GB001 in adult subjects with chronic rhinosinusitis

Rationale:

GB001 is a highly potent and 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, basophils, and epithelial cells (Kupczyk, 2017; Singh, 2017) as well as Group 2 innate lymphoid cells (ILC2) and T Helper cell type 2 (Th2) cells (Kato, 2019). GB001 is being developed as a once-daily oral add-on maintenance treatment for patients with moderate to severe eosinophilic asthma and related diseases.

The purpose of this Phase 2a study is to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of GB001 compared with placebo in patients with chronic rhinosinusitis with or without bilateral nasal polyps (NP).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of GB001 on the Sino-Nasal Outcome Test-22 (SNOT-22)	• Change from baseline to Week 16 in SNOT-22
Secondary	
• To evaluate the effect of GB001 on reducing opacification of the sinuses as measured by CT scan	• Change from baseline to Week 16 in opacification of sinuses as measured by Lund-Mackay score on CT scan
• To evaluate the effect of GB001 in the treatment of bilateral NP by assessment of the endoscopic nasal polyp score (NPS) in a subset of patients with nasal polyps	• Change from baseline to Week 16 in NPS • Time to first response (≥ 1 point improvement from baseline) in NPS
• To evaluate the effect of GB001 in improving patient reported symptoms	• Change from baseline to Week 16 in nasal congestion (NC) • Change from baseline to Week 16 in total symptom score (TSS)
• To evaluate the effect of GB001 in improving sense of smell (University of Pennsylvania Smell Identification Test, UPSIT)	• Change from baseline to Week 16 in UPSIT
• To evaluate the effect of GB001 on chronic rhinosinusitis (CRS) exacerbation	• Time to first CRS exacerbation, defined as deterioration of CRS symptoms requiring treatment with an antibiotic, an anti-inflammatory drug, or a symptom reliever; an Emergency Department visit; or hospitalization
• To evaluate the safety and tolerability of GB001 compared with placebo	• Incidence of treatment-emergent adverse events (TEAEs) • Change from baseline in laboratory, electrocardiogram (ECG), and vital signs parameters

Overall Design:

This is a Phase 2a, randomized, double-blind, placebo-controlled, multi-center study to evaluate GB001 in patients with chronic rhinosinusitis with or without bilateral nasal polyps (NP). A schematic of the study design is presented in Section 1.2. All subjects will be maintained on a stable background therapy of mometasone furoate nasal spray for the duration of the study.

Number of Subjects:

This study will randomize approximately 100 subjects, with approximately 50 per treatment group. Approximately 64 subjects will have presence of nasal polyps (chronic rhinosinusitis with nasal polyps [CRSwNP]), and approximately 36 subjects will have absence of bilateral NP (chronic rhinosinusitis without nasal polyps [CRSsNP]).

Intervention Groups and Duration:

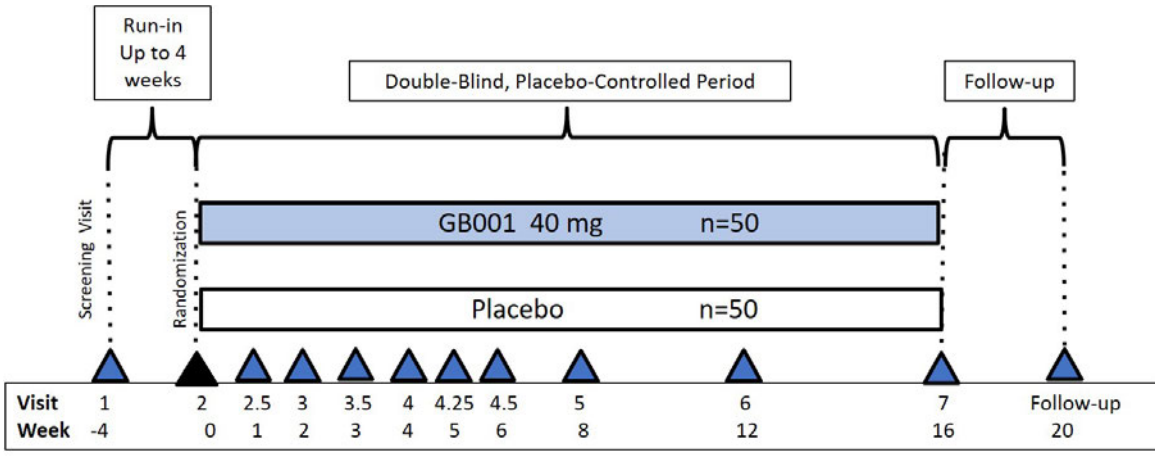
Treatment groups:

- GB001 40 mg once per day (QD)
- Matching placebo once per day (QD)

Total duration for study participation per subject is 24 weeks (includes a Screening visit; followed by up to 4-weeks Run-in period to allow for collection of baseline Diary data; a 16-week Double-Blind, Placebo-Controlled period; and 4-week Follow-up period).

Independent Data Monitoring Committee (IDMC): No

1.2. Schema



Note: Randomization will be stratified by country, the presence or absence of NP (CRSwNP and CRSsNP), and the presence or absence of comorbid asthma among CRSwNP subjects. The CRSwNP stratum will consist of approximately 64 subjects, and the CRSsNP stratum will consist of approximately 36 subjects.

1.3. Schedule of Activities

Procedure	Screening Visit	Randomization			Double-Blind Placebo-Controlled Period						Early Withdrawal from Study	Early Discontinuation of IP	Follow-up (after W16 or EW from study)	Notes
Visit	**1**	**2**	**2.5**	**3**	**3.5**	**4**	**4.25**	**4.5**	**5**	**6**	**7**	If needed	If needed	Follow up	
Week	**-4 to -2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	If needed	If needed	**20 or as needed**	Every visit window +/- 3 days (except for visit 3 which is +/- 2 days); The Screening period includes up to a 4 weeks Run-in period
Written informed consent	X														Consent form can be obtained prior to Visit 1.
Demography	X														
Medical history	X														History of nasal symptoms should be documented. See Section 5.1 inclusion criterion 5.
Surgical history	X														Specify type of surgery in source document and eCRF.
Prior treatment history	X														Specify surgery number, type, date.
Smoking and alcohol use history	X														
Concomitant medication	X	X	X	X	X	X			X	X	X	X	X	X	
Complete physical examination	X										X	X	X		
Assess presence of nasal polyps	X														Visual assessment to determine presence of nasal polyps by anterior examination.
Inclusion/exclusion criteria	X														
Randomization criteria		X													
Efficacy															
Sino-Nasal Outcome Test-22 (SNOT-22)	X	X				X			X	X	X	X	X		

Procedure	Screening Visit	Randomization			Double-Blind Placebo-Controlled Period						Early Withdrawal from Study	Early Discontinuation of IP	Follow-up (after W16 or EW from study)	Notes
Visit	**1**	**2**	**2.5**	**3**	**3.5**	**4**	**4.25**	**4.5**	**5**	**6**	**7**	If needed	If needed	Follow up	
Week	**-4 to -2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	If needed	If needed	**20 or as needed**	Every visit window +/- 3 days (except for visit 3 which is +/- 2 days); The Screening period includes up to a 4 weeks Run-in period
CT scan		X [1]									X	X*	X*		* Only if it occurs after visit 5. If CT scan cannot be completed on day of visit, it must be completed within 3 calendar days of visit. [1]Prior to 1st dose
Nasal endoscopy	X*	X*							X*		X*	X*	X*		*Only in subjects with presence of NP at screening by anterior examination.
Nitric oxide test		X		X					X		X	X	X		Nasal nitric oxide (nNO) and fractional exhaled nitric oxide (FeNO) will be measured.
University of Pennsylvania Smell Identification Test (UPSIT)		X									X	X	X		
Nasal symptoms assessment (review)		X				X			X	X	X	X	X		See Section 8.1.4
Visual Analog Scale (VAS)		X				X			X	X	X	X	X		
Asthma Control Questionnaire (ACQ-5)		X							X		X	X	X		Only in subjects with asthma (Section 10.8)
CRS exacerbation review	X	X	X	X	X	X			X	X	X	X	X	X	See Section 8.1.6
Safety															
AE/SAE recording (if any)	*	X	X	X	X	X			X	X	X	X	X	X	*See Section 8.3.2
12-lead electrocardiogram	X										X	X	X		See Section 8.2.3
Vital signs	X*	X	X	X	X	X			X	X	X	X*	X*	X	*Height and weight to also be measured
Laboratory Testing															
Pregnancy test (women of child-bearing potential only)	S	U		U		U			U	U	U	U	U	U	S = Serum U = Urine. If urine is positive, collect serum to confirm.

Procedure	Screening Visit	Randomization			Double-Blind Placebo-Controlled Period						Early Withdrawal from Study	Early Discontinuation of IP	Follow-up (after W16 or EW from study)	Notes
Visit	**1**	**2**	**2.5**	**3**	**3.5**	**4**	**4.25**	**4.5**	**5**	**6**	**7**	If needed	If needed	Follow up	
Week	**-4 to -2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	If needed	If needed	**20 or as needed**	Every visit window +/- 3 days (except for visit 3 which is +/- 2 days); The Screening period includes up to a 4 weeks Run-in period
Hematology with differential	X	X *							X		X	X	X	X	See Appendix 2 (Section 10.2).
Coagulation test (INR only)		X													See Appendix 2 (Section 10.2). *Includes INR at Visit 2
Hepatitis B surface antigen and Hepatitis C antibody	X														If Hepatitis C test is positive or indeterminant, a confirmatory test will be reflexively performed to confirm the results.
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Appendix 2 (Section 10.2), Table 4 and Appendix 6 (Section 10.6). Includes total bile acids at every visit. If ALP > 1xULN, include fractionation of ALP
Urinalysis	X										X	X	X		See Appendix 2 (Section 10.2).
Nasal mucosal lining fluid sample		X							X		X	X	X		See Section 8.6.1.
Pharmacokinetic (PK) sample						X				X	X	X	X		Subject to record time of last morning dose taken at home prior to Week 4, 12, and 16 visits. For Week 4, 12, and 16 visits, subject to bring the dose to clinic to be taken after the PK blood draw. See Section 8.5. At Week 4 visit, an additional PK sample will be taken at approximately 2.5 hours post-dose.
Biomarker sample (blood, urine)		X							X		X	X	X		See Sections 8.6.2 and 8.6.3.
RNA transcriptome research		X									X	X	X		See Section 8.6.3.

Procedure	**Screening Visit**	**Randomization**				**Double-Blind Placebo-Controlled Period**						**Early Withdrawal from Study**	**Early Discontinuation of IP**	**Follow-up (after W16 or EW from study)**	**Notes**
Visit	**1**	**2**	**2.5**	**3**	**3.5**	**4**	**4.25**	**4.5**	**5**	**6**	**7**	If needed	If needed	Follow up	
Week	**-4 to -2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	If needed	If needed	**20 or as needed**	Every visit window +/- 3 days (except for visit 3 which is +/- 2 days); The Screening period includes up to a 4 weeks Run-in period
Pharmacogenetic sample		X *				*			*	*	*				* If consent provided, sample can be collected at any visit post-randomization or any bio-sample used for this purpose; see Section 8.7.
Other Administrative Procedures															
Dispense investigational product (IP)		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			
Dispense MFNS for use as background therapy	X	X				X			X	X	X				
Instruct subjects on Diary use, if all screening eligibility criteria are met		<==========>													Eligible subjects enter the Run-in period and complete morning and evening Diary until Week 20.
Review Diary		X		X		X			X	X	X	X	X	X	
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: CRS = chronic rhinosinusitis; CT = computed tomography; eCRF = electronic case report form; EW = early withdrawal; IP =investigational product; MFNS = mometasone furoate nasal spray; RNA = ribonucleic acid.

2. INTRODUCTION

2.1. Study Rationale

GB001 is a highly potent and 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, basophils, and epithelial cells (Kupczyk, 2017; Singh, 2017) as well as Group 2 innate lymphoid cells (ILC2) and T Helper cell type 2 (Th2) cells (Kato, 2019). GB001 is being developed as a once-daily oral add-on maintenance treatment for patients with moderate to severe eosinophilic asthma and related diseases, and for patients with chronic rhinosinusitis with or without nasal polyps (NP).

The purpose of this study is to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of GB001 compared with placebo in patients with chronic rhinosinusitis with or without bilateral NP.

2.2. Background

Chronic rhinosinusitis (CRS) is defined as any inflammatory condition of the paranasal sinuses and associated nasal mucosa for more than 12 weeks (Fokkens, 2007). The loss of epithelial barrier function plays an essential role in the pathogenesis of CRS, with the loss of tight junctions permitting access to the sinus stromal tissue by allergens, bacteria, and bacteria-derived antigens. Clinical symptoms include nasal obstruction and congestion, reduction in or loss of sense of smell, anterior and posterior rhinorrhea, and facial pain. These symptoms can impact greatly upon a patient's quality of life.

Current recommendations for phenotyping CRS are based on the presence of nasal polyps (chronic rhinosinusitis with nasal polyps [CRSwNP]) or absence of nasal polyps (chronic rhinosinusitis without nasal polyps [CRSsNP]) (Fokkens, 2007). In a multinational study undertaken by the Global Allergy and Asthma European Network, the total prevalence of CRSwNP and CRSsNP has been estimated at 15.5% and 10.9% in the USA and Europe, respectively (Collins, 1997; Hastan, 2011). Patients with CRSwNP and comorbid asthma (~30%) have a poor therapeutic response and a high recurrence rate, and their disease tends to be more resistant to treatment (Thomas, 2008; Fokkens, 2007).

Within the group of patients with aspirin sensitivity, nasal polyps are found in 36% to 60% of patients. Patients with aspirin sensitivity, asthma, and NP, also known as aspirin-exacerbated respiratory disease (AERD), are usually non-atopic and the disease prevalence increases over the age of 40 years. Notably, these patients have an increased expression of DP_2 (Rothenberg, 2017). Eicosanoid changes in paranasal sinus diseases, including AERD, are generally characterized by an up-regulation of cysteinyl leukotrienes (CysLTs), lipoxin A4 (LXA4), and prostaglandin D2 (PGD_2) and a down-regulation of cyclooxygenase 2 (COX-2) and prostaglandin E2 (PGE_2).

Classification of CRS by nasal polyp phenotype is based on the observation that nasal polyp disease is more likely to be associated with an eosinophil-mediated Th2-high (IL-4, IL-5, and IL-13) cytokine profile. In contrast, CRSsNP is thought to present as a non-eosinophilic disease (Crombruggen, 2011). Emerging data, however, suggest that NP status alone can often be inadequate for defining a Th2-high/IL-5–high eosinophilic phenotype (Tan, 2017). The Tan

study examined tissue concentrations of IL-5 and eosinophil cationic protein (ECP) as surrogate markers for tissue eosinophilia. While values were significantly greater in patients with CRSwNP, there was extensive overlap in ECP concentrations between patients with and without NPs. Similarly, in a cluster analysis, expression of IL-5 in patients with CRS was identified in clusters with and without NPs (Tomassen, 2016).

Within these two groups, CRSwNP and CRSsNP, patients with an eosinophilic phenotype, eosinophilic CRS (eCRS) have a subtype of chronic sinusitis that is thought to occur secondary to chronic and systemic eosinophil activation. Patients with eCRS show overlapping mechanisms for eosinophilia and tend to have a poor response to medical and surgical management (Ferguson, 2004). In a recent cross-sectional study of adult patients with CRS (N = 345) undergoing endoscopic sinus surgery, eCRS was defined by histopathological assessment showing > 10 eosinophils/high-power field on sinus mucosal biopsy. Blood tests were performed preoperatively and assessed for a full blood count including eosinophils as well as markers of inflammation and atopy. Comparisons between eCRS and non-eCRS patients were performed. Among all cases with CRS, 60% were identified as eCRS, of which 41% had asthma and 47% had nasal polyps. Receiver operating characteristic (ROC) curve analysis predicted high tissue eosinophilia at blood eosinophil levels ≥ 240 cells/µL (sensitivity 70.9%, specificity 78.4%, area under the curve [AUC]: 0.792, $p < 0.01$). There was no association with other markers of inflammation and atopy (Ho, 2018).

Evidence from treatment with biologics inhibiting Type 2 inflammation have demonstrated clinical benefits in patients with CRSwNP (Bachert, 2017; Bachert, 2016). The treatment effect of GB001 has been demonstrated in patients with asthma and particularly Type 2 inflammation. Specifically, in a Phase 2 study in Japanese subjects (Study PTR-36-201), GB001 reduced asthma worsening (32.7%, GB001 5 mg; 20.8%, GB001 20 mg) compared with placebo (52.8%, $p < 0.05$ for both dose levels). This effect was enhanced in subjects with eosinophils ≥ 300 cells/µL.

In a recent post-hoc analysis of 36 subjects 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 fractional exhaled nitric oxide (FeNO, < 35 and ≥ 35 ppb) and blood eosinophil (< 250 and ≥ 250/µL) subgroups (Ortega, 2019; Skolnick, 2019). In the overall population, GB001 had an effect on forced expiratory volume in 1 second (FEV1) at Day 28 (difference in mean change for GB001 versus placebo of 102 mL, n = 36). Changes in FEV1 were also observed in the high baseline FeNO (n=14) and high baseline eosinophil (n=11) subgroups (differences of 207 mL and 133 mL, respectively). These results suggest that GB001 influences lung function in subjects with markers of eosinophilic inflammation.

It is anticipated that GB001 has the potential to provide clinical benefit in patients with eosinophilic chronic rhinosinusitis.

2.3. Benefit/Risk Assessment

2.3.1. GB001 Benefit/Risk Assessment

GB001, an oral DP_2 antagonist, is being developed as a controller therapy in asthma. The clinical development of GB001 includes 9 completed clinical studies and 2 ongoing clinical studies.

As of 29 August 2019, a total of 459 subjects have received at least 1 dose of GB001 at any dose level. Of these, 98 subjects received a single dose of GB001 ranging from 1 mg to 200 mg, and 361 subjects received multiple doses from 5 mg to 160 mg. Of the 361 subjects who received multiple doses, about half (n = 159) were subjects with asthma in the completed Phase 2 studies who received either GB001 20 mg for up to 12 weeks, including 2 weeks with concurrent dosing of montelukast 10 mg daily (Study ADC3680-07), or GB001 22.73 mg daily for up to 4 weeks (Study ADC3680-04) or up to 16 weeks concurrent with ICS withdrawal and discontinuation (Study PTR-36-201).

Based on evaluation of asthma worsening (Study PTR-36-201), GB001 at a 20 mg dose showed efficacy in the overall population and the greatest efficacy in the subgroup of patients with eosinophil counts ≥ 300 cells/μL. This is consistent with the current understanding of the biology regarding this pathway.

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 Study GB001-2001 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.

In a study with another DP_2 antagonist (OC000459) which evaluated 35 subjects allergic to grass pollen, subjects were exposed to grass pollen for 6 hours on the 2nd and 8th days of treatment. During the first treatment period, there was a significant reduction in the total nasal symptom score compared with placebo (Horak, 2012). These data support the role of DP_2 in upper airway disease and provide a foundation for potential therapeutic benefits by blocking this pathway in patients with upper airway inflammatory disease.

2.3.2. Study Design Benefit/Risk Assessment

This study is designed to assess the effect of GB001 on the Sino-Nasal Outcome Test-22 (SNOT-22) in comparison to placebo.

To minimize any potential risk to subjects, stringent criteria are utilized during screening to exclude subjects with a history of significant comorbidities that could impact subjects' safety. All participating subjects on active or placebo will be frequently and closely monitored during the study with optimized standard of care.

This study proposes to minimize the number of subjects to be exposed to GB001, while still being able to assess potential effects on CRS disease. Based upon the study design and the close monitoring from the Sponsor and/or designee, the benefits of participation in GB001-2101 outweigh the potential risks of exposure to GB001. The study will provide the basis of a first benefit/risk assessment of GB001 in patients with chronic rhinosinusitis with or without bilateral nasal polyps.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of GB001 on the Sino-Nasal Outcome Test-22 (SNOT-22)	• Change from baseline to Week 16 in SNOT-22
Secondary	
• To evaluate the effect of GB001 on reducing opacification of the sinuses as measured by CT	• Change from baseline to Week 16 in opacification of sinuses as measured by Lund-Mackay score on CT
• To evaluate the effect of GB001 in the treatment of bilateral NP by assessment of the endoscopic nasal polyp score (NPS) in a subset of patients with nasal polyps	• Change from baseline to Week 16 in NPS • Time to first response (≥ 1 point improvement from baseline) in NPS
• To evaluate the effect of GB001 in improving patient reported symptoms	• Change from baseline to Week 16 in nasal congestion (NC) • Change from baseline to Week 16 in total symptom score (TSS)
• To evaluate the effect of GB001 in improving sense of smell (UPSIT)	• Change from baseline to Week 16 in UPSIT
• To evaluate the effect of GB001 on chronic rhinosinusitis (CRS) exacerbation	• Time to first CRS exacerbation, defined as deterioration of CRS symptoms requiring treatment with an antibiotic, an anti-inflammatory drug, or a symptom reliever; an Emergency Department visit; or hospitalization
• To evaluate the safety and tolerability of GB001 compared with placebo	• Incidence of treatment-emergent adverse events (TEAEs) • Change from baseline in laboratory, ECG, and vital signs parameters
Exploratory	
• To evaluate the effect of GB001 on symptom improvement as measured by a visual analog scale (VAS)	• Change from baseline to Week 16 in VAS
• To evaluate the effect of GB001 on CRS exacerbation rate	• Annualized rate of CRS exacerbations

Objectives	Endpoints
• To evaluate the effect of GB001 on maxillary CT opacification	• Change from baseline to Week 16 in percentage of maxillary sinus volume occupied by disease on CT scan
• To evaluate the effect of GB001 on worsening of CRS requiring the use of antibiotics	• Proportion of subjects with antibiotic use due to worsening CRS by Week 16
• To evaluate pharmacokinetics (PK) of GB001	• Plasma concentration of GB001
• To evaluate the effect of intervention on, as a function of, the pharmacodynamic markers (PD)	• Correlation between baseline markers and safety, tolerability, and efficacy parameters • Change in PD markers over time
• To evaluate the relationship between safety, efficacy, and exposure parameters and pharmacogenetics (PGx)	• Correlation between baseline characteristics and single nucleotide polymorphisms • Change from baseline in safety, efficacy, and exposure parameters as a function of single nucleotide polymorphisms

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, multi-center study to evaluate GB001 administered once a day for 16 weeks in subjects with chronic rhinosinusitis with or without bilateral nasal polyps.

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

4.1.1. Study Design

Prior to screening, subjects must be on a stable regimen of intranasal corticosteroids (INCS) for ≥ 2 months. If the subject is using an INCS product other than mometasone furoate nasal spray (MFNS) prior to the Screening visit, the Investigator must switch the subject to MFNS at the Screening visit. All subjects will be maintained on a stable background therapy of mometasone furoate nasal spray for the duration of the study.

Screening Visit (Visit 1): 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, if necessary. All other screening procedures should be completed, where possible, 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). The Run-in period commences with completion of all Screening visit procedures and concludes at the Randomization visit (Visit 2). During the Run-in period of up to 4 weeks, subjects will capture nasal symptoms and MFNS use in a Diary daily (morning and evening):

- Subject's treatment regimen with MFNS should remain stable.
- 2 actuations (50 µg/actuation) in each nostril twice daily (total daily dose of 400 µg), unless subject is intolerant to a twice daily (BID) regimen of MFNS in which case, they can stay on the dose regimen in place prior to screening.
- The only dose modification of MFNS during the Run-in period may be for subjects who were switched from another INCS to MFNS and need to change to a QD regimen due to intolerability.

Randomization Visit (Day 1/Week 0/Visit 2): Subjects who meet the randomization eligibility criteria will be randomized in a 1:1 ratio to receive one of the following double-blind treatments for 16 weeks:

- GB001 40 mg once per day (QD)
- Matching placebo once per day (QD)

Randomization will be stratified by country, the presence or absence of NP (CRSwNP and CRSsNP), and the presence or absence of comorbid asthma among CRSwNP subjects. Presence of NP is defined by a minimum NPS of 4 out of a maximum score of 8 with a score of at least 2 for each nostril. Absence of NP is defined as an absence of NP based on visual examination or an NPS of 0 based on nasal endoscopy. Presence of comorbid asthma is defined as a diagnosis of asthma by a physician according to Global Initiative for Asthma (GINA) guidelines at screening

or prior to study entry. The CRSwNP stratum will consist of approximately 64 subjects, and the CRSsNP stratum will consist of approximately 36 subjects.

Subjects will continue on mometasone furoate: MFNS two actuations in each nostril BID (or QD in case subject cannot tolerate the high dose) during the course of the study.

Following initiation of investigational product (IP) at the clinic, subjects will visit the clinic weekly for the first 6 weeks and approximately every 4 weeks thereafter through week 20, for a total of 10 additional visits (refer to Schedule of Activities, Section 1.3).

Early Discontinuation of IP and Early Withdrawal from Study: Subjects will be requested to attend the Early Discontinuation of IP or Early Withdrawal (EW) visit, as appropriate, 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 visit sequence. At the visits after the Early Discontinuation of IP visit, study procedures will be completed except for dispensation/return of IP. Subjects who withdraw early from the study, regardless of the reason, will be requested to return to the clinic to complete the EW visit. All subjects who remain on IP through and including Visit 7 (Week 16) or who complete the EW visit will be asked to return for a Follow-up visit approximately 4 weeks after their last dose of IP to assess subject safety.

Follow-up Period: Subjects can continue treatment with the stable dose of MFNS maintained over the Double-Blind, Placebo-Controlled period, or modify treatment based on medical judgment.

Total duration for study participation per subject is up to 24 weeks (includes a Screening visit, followed by an up to 4-weeks Run-in period to allow for collection of baseline Diary data; a 16-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, or evaluation of an AE. Any procedure that is conducted during a regularly scheduled on-treatment visit may be performed at an unscheduled visit.

4.2. Scientific Rationale for Study Design

4.2.1. Study Population

The study population is comprised of: symptomatic CRS subjects with CRSsNP, defined as an absence of NP based on visual examination or an NPS of 0 based on nasal endoscopy, and evidence of an eosinophilic phenotype (eCRS), defined as a blood eosinophil count of ≥ 250 cells/μL; and symptomatic CRS subjects with CRSwNP, defined as a minimum NPS of 4 out of a maximum of 8, with at least a score of 2 for each nostril, as assessed by endoscopic diagnosis by a blinded central reader. Subjects with historical evidence of neutrophilic predominant polyp disease will be excluded considering that the mechanism of action of GB001 is thought to be linked to eosinophilic Type 2 inflammation. The overall study population will consist of approximately 64 CRSwNP subjects and 36 CRSsNP subjects.

GB001 will be administered as an additional treatment on top of a stable standard of care (SOC) regimen of mometasone furoate nasal spray (MFNS).

4.2.2. Choice of Control Group

All subjects will be on background SOC. The study is placebo-controlled to minimize bias and provide an inactive control group to which the efficacy of GB001 can be compared. Comparisons between the GB001 and placebo treatment groups will facilitate differentiation of the GB001 safety profile from that of the SOC. Lastly, a placebo group, as opposed to an active control, will help to understand whether the occurrence of an AE in the GB001 group is different from that which would occur in this population in the absence of GB001.

4.2.3. Efficacy Endpoint Selection

The primary endpoint is the change from baseline to Week 16 in SNOT-22. This instrument has been used in multiple clinical studies to demonstrate the impact of different types of treatment interventions in subjects with CRS.

In addition, this study will explore the impact of GB001 on bilateral nasal polyps and associated sinus symptoms, using specific assessments and questionnaires.

4.3. Justification for Dose

This study will assess 40 mg of GB001 in adult subjects with chronic rhinosinusitis with or without bilateral nasal polyps. In a previous asthma study (PTR-36-201), GB001 5 mg and 20 mg doses were evaluated. While both doses of GB001 were effective compared to placebo in decreasing the proportion of subjects with asthma worsening/exacerbations in a treatment withdrawal design, the 20 mg dose produced 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, Asthma Control Questionnaire (ACQ-5), and time to asthma worsening relative to placebo. However, no improvements in lung function were observed, suggesting that higher doses are needed to achieve clinical benefit across different endpoints, including lung function. A comparable safety profile was observed across all treatment arms (including placebo) in this study. Considering that patients with chronic rhinosinusitis with eosinophilic inflammation manifest with more inflammation and disease severity than patients with asthma in general, a dose of 40 mg should be adequate and safe to investigate the efficacy and safety of GB001 in this patient population. The selection of this dose encompasses the totality of PK, efficacy, and safety data of GB001 available to date.

4.4. End of Study Definition

Subjects will be regarded to have completed the study if he/she completes the Week 16 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

Prior to randomizing a subject, additional randomization criteria in Section 5.3 must be met.

Subjects are eligible to enter the Run-in period only if all of 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 to 75 years of age at the time of Screening visit.
3. **Sex:** 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. **Diagnosis:** Diagnosis of chronic rhinosinusitis with or without bilateral nasal polyps for at least 12 weeks prior to Visit 1.
5. **Nasal symptoms:** Presence of at least two of the following symptoms prior to Visit 1:
    - nasal blockade/obstruction/congestion
    - nasal discharge (anterior/posterior nasal drip)
    - facial pain/pressure
    - reduction or loss of smell
6. **INCS:** Subjects must be on a stable administration of intranasal corticosteroids (INCS) for ≥ 2 months prior to Visit 1. For subjects using a specialized delivery device (eg, XHANCE™) or corticosteroids administered via irrigation (eg, budesonide + sterile saline), they must be on MFNS for ≥ 2 weeks prior to screening.

5.2. Exclusion Criteria

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

1. **Nasal symptoms:** SNOT-22 score < 20 as assessed at screening.
2. **Prior polyp surgery:** Subjects who have undergone any nasal surgery (excluding polypectomy performed as an outpatient procedure) within 4 months before screening or have had ≥ 4 sinonasal surgeries in the past.
3. **Comorbidities:** Presence of a known pre-existing clinically important condition including: active tuberculosis, pulmonary fibrosis, bronchopulmonary aspergillosis, eosinophilic granulomatous polyangiitis (Churg-Strauss syndrome), Young's syndrome, Kartagener's syndrome or dyskinetic ciliary syndromes, and cystic fibrosis. 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.

4. **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).
5. **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.
6. **Prior anti-inflammatory treatment:** Subjects who have required a burst of systemic corticosteroids (eg, oral, intravenous, intramuscular corticosteroids) within the 1 month before screening or are scheduled to receive systemic corticosteroids during the study period for another condition, or who have required intranasal corticosteroid drops within 1 month prior to screening.
7. **Intolerant to mometasone furoate nasal spray.**
8. **Specific conditions/concomitant diseases:** Subjects with conditions such as: antrochoanal polyps, nasal septal deviation that would occlude at least one nostril; acute sinusitis, invasive fungal rhinosinusitis, neutrophilic polyposis, nasal infection or upper respiratory infection at screening or in the 2 weeks before screening. Subjects requiring chronic systemic antibiotic treatment for rhinosinusitis.
9. **Ongoing rhinitis medicamentosa.**
10. **ECG Assessment:** Subjects with QTcF ≥ 450 msec for males or QTcF ≥ 470 msec for females on the Screening visit ECG. However, if QTcF is above this prespecified limit and there are no other clinically significant ECG abnormalities in the opinion of the Investigator, the assessment can be repeated in triplicate. The triplicate QTcF values should be averaged by the Investigator to determine eligibility of the subject to enter the Run-in period. However, if any of the triplicate ECGs show a clinically significant abnormality in the opinion of the Investigator, the subject should be excluded, regardless of the average QTcF of the triplicates.
11. **Alcohol/Marijuana/Illicit Drugs/Substance Abuse:** A known or suspected history of alcohol misuse, marijuana, illicit drugs, or substance abuse within 12 months prior to Screening visit.
12. **Smoking history:** Asthma or COPD patients that are current smokers (any substance), or former smokers with a smoking history of ≥ 10 pack-years [(number of cigarettes per day/20) × 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.
13. **Immunodeficiency:** A known immunodeficiency, including that due to human immunodeficiency virus (HIV), other than that explained by systemic corticosteroid use.
14. **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).

15. **Receiving prohibited medications:** Refer to Appendix 10 (Section 10.10) 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
    c. Medications, food or drink that are moderate or strong CYP3A4 inhibitors or inducers
    d. Other medications that have the potential for interaction with GB001
    e. Medications that have a black-box warning for hepatic toxicity.
16. **Prior participation in a study with GB001:** Subjects who previously participated in a study with GB001 (also named PTR-36 or ADC3680).
17. **Hypersensitivity:** A known sensitivity to GB001 or any of its excipients. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption. Subjects with mild-moderate lactose intolerance are not excluded. Subjects with sensitivity or intolerance to aspirin (ie, subjects with aspirin-exacerbated respiratory disease [AERD] with or without desensitization).
18. **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.
19. **Adherence:** Subjects who have a known lack of adherence to medications such as INCS.
20. **Body Mass Index (BMI):** BMI is ≥ 40 kg/m^2.
21. **Participation**: Subject has any other condition or reason that, in the opinion of the Investigator, would prohibit the subject from participating in the study.
22. **Participation in another clinical study**: Subjects currently participating in an interventional clinical study with a biologic agent or who have received study drug in another clinical study are not to be considered for participation until the completion of the safety follow-up visit or following a non-investigational drug period of no less than five half-lives. Subjects may not participate in another interventional clinical trial while enrolled in this study.

5.3. Randomization Criteria

Subjects must fulfill the following criteria to be randomized to study treatment:

1. **Diary compliance:** Compliance with completion of the Diary as defined as:
   a. Completion of questions on 4 or more of the last 7 days immediately prior to Visit 2 (includes the morning of Visit 2).
   b. **Note:** If the Diary 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 Diary parameters above.
2. **Eosinophilic Phenotype:** Subjects must meet at least one of the criteria below.
   - Blood eosinophil count ≥ 250 cells/µL obtained at Visit 1.
     OR
   - Minimum NPS of 4 out of a maximum score of 8 with a score of at least 2 for each nostril as assessed by a blinded central reader. Subjects with an NPS of 1-3 are not eligible for randomization.
3. **CRS exacerbation**: Subjects who experience a CRS 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 status. If a 4-week Run-in period has elapsed before the subject is back to baseline status, then the subject will be considered a Run-in failure. CRS exacerbation is defined in Section 8.1.6.
4. **Laboratory abnormality:** No evidence of clinically significant abnormality in the hematological, biochemical, or urinalysis at Screening visit, as judged by the investigator.
5. **Hepatitis status:** No diagnosis of chronic hepatitis B or C, as evidenced by a negative hepatitis B surface antigen (HBsAg) or hepatitis C antibody screen at Screening visit.
6. **Chemistry and hematology obtained at Screening visit:**
   - ALT ≤ 1 × the upper limit of normal (ULN)
   - AST ≤ 1 × ULN
   - Alkaline phosphatase < 2 × ULN
   - Bilirubin < 1 × ULN
   - Absolute eosinophil count < 1,500 cells/µL
   - White blood cell count < 15,000 cells/µL
7. **Pregnancy test:** For WOCBP, both the serum pregnancy test at the Screening visit and the urine pregnancy test at Visit 2 must be negative.
8. **Use of MFNS**: Subject newly switched onto MFNS during screening should tolerate MFNS during Run-in.
9. **Nasal symptoms:** SNOT-22 score ≥ 17 as assessed at randomization.
10. **ECG overread:** ECG overread by the central ECG reader confirms the QTcF interval is < 450 msec for males or QTcF < 470 msec for females.

5.4. Screen or Run-In Failures

Subjects will be assigned a subject number at the time of signing the ICF and entry into the online registration system (IRT). 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 Sponsor and/or designated Medical Monitor. A new subject number will be assigned if approved to rescreen. One rescreen is permitted.

6. INVESTIGATIONAL PRODUCT

6.1. Investigational Product Administered

Table 1: Investigational Product Formulation by Treatment Group

Treatment Groups	**GB001 40 mg**	**Placebo**
Dose Formulation	20 mg Film-Coated Tablet	Matched Placebo Film-Coated Tablet
Unit Dose Strength(s)	2 × 20 mg tablet	2 × placebo tablet
Dosage Level(s)	40 mg	Placebo
Route of Administration and Instructions	Oral, in the morning on an empty stomach[a]	Oral, in the morning on an empty stomach[a]
Packaging and Labeling	GB001 and placebo film-coated tablets will be packaged in a blinded manner in high-density polyethylene (HDPE) 50 mL bottles. The bottles 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.	

[a] No food intake. Liquids are acceptable.

6.2. 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 IP. All IP 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.

6.3. Randomization and Blinding

6.3.1. Randomization

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

Randomization will be stratified by country, the presence or absence of NP (CRSwNP and CRSsNP), and the presence or absence of comorbid asthma among CRSwNP subjects. Presence of NP is defined by a minimum NPS of 4 out of a maximum score of 8 with a score of at least 2 for each nostril. Absence of NP is defined as an absence of NP based on visual examination or an NPS of 0 based on nasal endoscopy. Presence of comorbid asthma is defined as a diagnosis of asthma by a physician according to Global Initiative for Asthma (GINA) guidelines at screening or prior to study entry. The CRSwNP stratum will consist of approximately 64 subjects, and the CRSsNP stratum will consist of approximately 36 subjects.

6.3.2. Assignment of Investigational Product Bottle Numbers

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

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

6.3.3. Unblinding of an Individual Subject

The IRT system will be programmed with blind-breaking instructions. In case of a medical emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator, when possible, should make 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.

Up to 3 Sponsor individuals not directly involved in the conduct of the study may access unblinded individual subject treatment assignments during the course of the study for the purpose of performing informal analyses to inform further development of GB001. No modifications will be made to the study based on this unblinded access, and there will be no communication of any analyses performed or their results outside of these designated Sponsor individuals. Subjects, investigators and other site personnel, and Sponsor (or designee) personnel who are directly involved in the conduct of the study will remain blinded to treatment assignments until after the completion of the study and the database has been locked.

[redacted]

6.4. Investigational Product Compliance

For additional details refer to Study Reference Manual and/or Pharmacy Manual.

IP accountability will be assessed at each visit by counting returned tablets. Deviation(s) from the prescribed dosage regimen will be evaluated per guidelines provided in the Study Reference Manual and the Pharmacy Manual. Subjects who demonstrate poor IP compliance, in the opinion of the Investigator, 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. For additional details refer to Study Reference Manual and Pharmacy Manual.

6.5. Concomitant Therapy

Subjects should remain on their stable dosing treatment (mometasone furoate [eg, NASONEX® or a generic such as other mometasone furoate nasal sprays (eg, as available from Apotex Corp, Amneal Pharmaceuticals, LLC, Sandoz Inc)] 50 micrograms/actuation Nasal Spray) for the duration of their time on study. If a subject discontinues from IP or withdraws from the study due to lack of efficacy, SOC therapy should not be adjusted until after the Safety Follow-up visit.

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.

6.5.1. Prohibited and Restricted Medications Prior to the Screening Visit and Throughout the Study

Please refer to Appendix 10 (Section 10.10) for prohibited and restricted medications and other treatments.

6.6. 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.

6.7. Intervention After the End of the Study

There is no plan for intervention following the end of the study.

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Investigational Product

Permanent discontinuation of IP does not mean withdrawal from the study, and the subject will be encouraged to remain in the study and continue to complete all study visits and diaries as per the SoA (Section 1.3). If a subject permanently discontinues IP prior to Visit 6 (Week 12) and remains in the study through Visit 7 (Week 16), the subject will not need to return for the Follow-up Visit (Week 20) as the Week 16 Visit will serve as an acceptable Follow-up visit.

Mandatory criteria for permanent discontinuation of IP are documented in Appendix 6 Section 10.6. A subject must permanently discontinue IP if the subject experiences a drug-induced liver disorder.

For subjects who simultaneously discontinue IP and withdraw early from the study, the EW Visit procedures should be conducted (Section 1.3), and a separate Early Discontinuation of IP Visit is not needed. The subjects should be encouraged to return for the Follow-up Visit.

7.1.1. Pregnancy

A subject must permanently discontinue IP if the subject becomes pregnant. See Appendix 4 Section 10.4 and Section 8.3.5 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.

7.1.2. Liver Safety

A subject must permanently discontinue IP if the subject meets the liver chemistry criteria that are specified in Appendix 6 Section 10.6.

7.2. Subject Withdrawal from the Study

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

- Physician decision
- Adverse event
- Noncompliance with study drug
- Withdrawal by subject
- Study terminated by the 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.

If a subject is withdrawn from the study and has previously discontinued IP, if possible, the EW Visit should be conducted, as shown in the SoA (Section 1.3). If the subject is simultaneously discontinuing IP and withdrawing early from the study, the EW visit should be conducted. The subjects should be encouraged to return for the Follow-up Visit. See SoA for data to be collected at the time of study withdrawal and at follow-up and for any further evaluations that need to be completed.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

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 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. The subject's data and biosamples may still be assayed, in accordance with his/her original informed consent.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- 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, 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):

(The list may not be all inclusive. Review the SoA and the Study Reference Manual for additional guidance)

- Informed consent
- Demography
- Administer SNOT-22
- Medical/surgical history
- Concomitant medication review including confirmation of INCS use for more than 8 weeks prior to screening
- Vital signs
- Physical exam including visual exam of nose for polyps
- 12-lead electrocardiogram
- Review of inclusion/exclusion criteria
- Collect urine and blood samples
- Record adverse events, if any
- Dispense Diary and train subject in its use including responding to the morning and evening CRS symptom questions and daily MFNS use
- Ensure subject has MFNS (or equivalent for non-US sites) for use as required background therapy throughout the study.
- Perform nasal endoscopy (subset of subjects). Endoscopy (including use of decongestants and/or anesthetics before the procedure) will be performed after all other efficacy assessments have been completed at each visit; video sequences will be downloaded by the investigator to the blinded central reader's secure Internet site. For eligibility in the CRSwNP stratum, blinded central reading of the Visit 1 endoscopy will be used.
- Remind patient to bring diary materials to the next visit
- Complete eCRF

Note: During the Run-in period, the site should review the central endoscopy overread report and the laboratory results. If the overread or laboratory results indicate that the subject is not eligible for randomization, the subject should be contacted to return all study provided materials to the site.

Randomization Visit (Visit 2):

(The list may not be all inclusive. Review the SoA and the Study Reference Manual for additional guidance)

- Review Diary to assess eligibility and remind subject to bring the materials to the next visit
- Review randomization eligibility criteria including results from blinded central reader of Visit 1 nasal endoscopy to confirm entry criteria
- Have subject complete questionnaires including SNOT-22
- Concomitant medication and adverse event review
- Vital signs
- Reconfirm eligibility based on review of Inclusion/Exclusion Criteria (Section 5.3)
- Collect lab samples
- Perform CT scan. If a qualifiable CT scan has been performed within 30 days on the qualified equipment consistent with the study imaging protocol and allowing appropriate interpretation/assessment and the image sequences are available for upload to the imaging core laboratory, then a CT scan on Visit 2 is not required. If a historic CT scan is to be used this CT scan must be uploaded to the Imaging Core Laboratory at a minimum of 14 days prior to the randomization visit to ensure image quality and appropriate quantification.
- Perform nasal endoscopy (only on subjects categorized as CRSwNP)
- Perform nitric oxide measurements on all subjects.
- Dispense IP
- Complete eCRF

8.1. Efficacy Assessments

8.1.1. SNOT-22

The SNOT-22 (Section 10.9) is a validated questionnaire to assess the impact of chronic rhinosinusitis on quality of life and utilizes a 2-week recall period. It is a 22-item outcome measure on a 5-point category scale applicable to sinonasal conditions and surgical treatments. The total scores range from 0 to 110 with higher total scores implying greater impact of CRS on quality of life. A Minimal Clinically Important Difference (MCID) is available: 8.90 (Hopkins, 2009).

8.1.2. Computer Tomography (CT)

CT of the sinuses will be performed at Randomization, at end of treatment (Visit 7) and if a patient is withdrawn early.

For the accurate assessment of Lund-Mackay scores and 3D volumetric measurement of the maxillary sinus, the same acquisitions (sequences) will be performed and used for centralized imaging data assessments and scored by the imaging core laboratory.

Blinded central reading of the Visit 2 assessment will be used for comparison with the Week 16 visit. The final results of blinded central reading will be made available after the study.

Details on CT will be available in a separate operational manual provided to the sites.

The Lund-Mackay system is based on localization with points given for degree of opacification: 0 = normal, 1 = partial opacification, 2 = total opacification. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side. The osteomeatal complex is graded as 0 = not occluded, or 2 = occluded deriving a maximum score of 12 per side (Lund, 1993). This scoring system has been validated in several studies (Scadding, 2011; Hopkins, 2009).

For subjects in whom the osteomeatal complex (OC) is missing (because of a previous surgery) the blinded central reader should consider the location of the former OC and provide a scoring (as if the OC was there).

Three-Dimensional volumetric measurement of the maxillary sinus will be performed at the imaging core laboratory.

This method is used to calculate:

- volume of the air (mL)
- volume of mucosa (mL)
- percent occupied by disease
- thickness of lateral wall

For the analysis, blinded central reading of the CT at Visit 2 will be used for comparison with Week 16. The sites will remove subject-identifying information from the imaging data header prior to sending the imaging data to the imaging core laboratory. The percent change in opacification from baseline to end of treatment will be calculated (Van Agthoven, 2001).

If a prior CT within 60 days of the Randomization visit is available and the Imaging Core Laboratory confirms their quality criteria are met, this CT may be acceptable.

8.1.3. Bilateral Endoscopic Nasal Polyp Score

The bilateral endoscopic nasal polyp score (NPS) is the sum of the right and left nostril scores, as evaluated by means of blinded, centrally read nasal endoscopy. NP is graded based on polyp size described in the Table 2 below:

Table 2: Endoscopic Nasal Polyp Score

Polyp Score	Polyp Size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity

Nasal endoscopy should be performed at the end of the scheduled visits and preceded by local administration of anesthetic drugs in combination with a decongestant. Standard video sequences will be downloaded or sent to the centralized reader. Centralized imaging data assessments and scoring by an independent physician reviewer for the imaging data will be performed for all endoscopies. To confirm eligibility at Visit 2 (baseline), only the Visit 1 blinded central reading will be made available to the site. The final results of blinded central reads will be made available after the study.

8.1.4. Disease-specific, Daily Symptom Assessments

On a daily basis, from Visit 1 and throughout the study, the subject will use a Diary to:

Respond to the morning and evening individual rhinosinusitis symptom questions using a 0–3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms) for the following symptoms:

- congestion and/or obstruction
- anterior rhinorrhea (runny nose)
- posterior rhinorrhea (post-nasal drip)
- loss of sense of smell

The Diary is provided at Visit 1 and information is collected on the days/times indicated in the Schedule of Activities. Diary entries are to be completed until the Follow-up visit (Week 20).

The TSS is the sum of the scores from the 4 symptom categories and ranges from 0–12. For each rhinosinusitis symptom category and the TSS, the average of the available scores recorded during the last 7 days before Visit 2 (up to 14 scores, including the morning of Visit 2) will be used to determine the baseline value. A minimum of 4 days of the previous 7 days must be completed (inclusive of the morning entry on the day of randomization) in order to qualify for randomization (see Section 5.3).

8.1.5. Smell Test: University of Pennsylvania Smell Identification Test (UPSIT)

The test consists of four booklets, each containing 10 odorants with one odorant per page (Doty, 1984). The test-time is about 15 minutes. The stimuli are embedded in 10–50 µm diameter plastic microcapsules on brown strips at the bottom of each page. Above each odorant

strip is a multiple-choice question with four alternative words to describe the odor. The subject is asked to release the odorant by rubbing the brown-strip with the tip of a pencil and to indicate which of four words best describes the odor. An UPSIT result is scored out of 40 where a higher score indicates better olfaction.

8.1.6. CRS Exacerbation

Chronic rhinosinusitis exacerbation is defined as deterioration of CRS symptoms requiring treatment with an antibiotic, an anti-inflammatory drug, or a symptom reliever; an Emergency Department visit; or hospitalization (Kuiper, 2018; Meltzer, 2006; Rosenfeld, 2015).

The date of onset of a CRS exacerbation will be considered to be the first date of treatment with an antibiotic, an anti-inflammatory drug, or a symptom reliever, the date of Emergency Department visit, or the date of hospitalization, whichever occurs first. The end date of a CRS exacerbation will be considered to be the last date of treatment with an antibiotic, an anti-inflammatory drug, or a symptom reliever, or 6 days after the date of onset (for a total duration of 7 days), whichever is later. Courses of treatment separated by 7 or more days will be counted as separate exacerbations.

8.1.7. Visual Analog Scale (VAS)

The visual analog scale (VAS) for rhinosinusitis is used to evaluate the total severity and is only validated in adult CRS to date (Fokkens, 2007). The subject is asked to indicate on a VAS the answer to the question: “How troublesome are your symptoms of rhinosinusitis?” The VAS ranks from 0 (Not troublesome) to 10 (Worst thinkable troublesome), see Appendix 7, Section 10.7.

The disease can be divided into Mild, Moderate, and Severe based on total severity VAS score (0 to 10 cm):

- Mild = VAS 0-3
- Moderate = VAS > 3–7
- Severe = VAS > 7–10

8.1.8. Nitric Oxide Measurement

Nitric oxide may be measured at the visits specified in the SoA utilizing equipment provided by a central vendor. Nitric oxide will be measured both by oral (fractional exhaled nitric oxide [FeNO]) and nasal (nasal nitric oxide [nNO]) methods. For more details, please refer to the Study Reference Manual.

8.1.9. Other Assessments

Asthma control will be assessed at visits (Visits 2, 5, and 7, EW, early discontinuation) using the ACQ-5 questionnaire. These assessments will be conducted only in subjects who reported a diagnosis of asthma at the Screening visit.

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 will be conducted as designated in the SoA (see Section 1.3).
- Height and weight will also be measured and recorded as noted in the SoA (see Section 1.3).

8.2.2. Vital Signs

- Pulse rate, respiratory rate, temperature, and blood pressure will be assessed.
- 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).
- 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.
- Vital signs will be measured prior to ECG measurements.

8.2.3. Electrocardiograms

- Assessment of a single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) to determine heart rate and measure PR, QRS, QT, and QTc intervals. The test can be repeated in triplicate if the QTcF value is slightly above the threshold.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed at the visits designated in the SoA. 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 abnormal and clinically significant 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 source document.

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

Treatment-emergent adverse events will be collected from the first dose of IP until the end of follow up. Serious adverse events will be collected beginning at the time of consent until the end of follow up. Medical occurrences that begin after obtaining informed consent and before the first dose of IP will be recorded on the Medical History/Current Medical Conditions section of the eCRF and not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately upon the site learning of an event and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (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 events of interest (defined in Section 10.3) 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).

8.3.4. 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 the 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 IB. The Investigator will then notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies 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.

8.3.6. Death Events

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

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

CRS exacerbation is an efficacy assessment that is a disease-related outcome not qualifying as an AE unless the investigator considers the CRS exacerbation to have met the definition of an SAE (Appendix 3; Section 10.3.2). CRS exacerbation meeting the definition of an SAE will be reported in the appropriate eCRF (Appendix 3; Section 10.3.5). CRS exacerbation not meeting the definition of an SAE should not be reported as an AE. CRS exacerbations, as captured by

efficacy assessment and by the occurrence of SAEs, will be monitored by the Sponsor 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 as specified in the SoA (see Section 1.3):

- At Week 4, 12, and 16 visits, PK samples will be collected at pre-dose during the visit. At Week 4 visit, an additional PK sample will be taken at approximately 2.5 hours post-dose.
- Subjects will be instructed to take their dose in the morning at their regular dosing time on the day prior to Week 4, 12, and 16 visits and to record the time of dosing on a paper worksheet.
- Subjects will be instructed not to take the dose in the morning on the day of Week 4, 12, and 16 visits and bring the dose with them for the visit. Subjects will take the dose in the unit following the pre-dose PK sampling during these 3 visits.

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

Nasal mucosal lining (airway) fluid, blood and urine samples may be collected at the designated times specified in the SoA (see Section 1.3) and may be used for multiple exploratory assays to evaluate the placebo-corrected effect of GB001 on potential target engagement, PD biomarkers (eg, Th2 pathway activity, lymphocyte subsets, vitamin D, etc.), safety, tolerability, and efficacy parameters.

Residual blood, airway, and urine samples may be stored for additional future assays that may elucidate response to GB001. 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.

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

8.6.1. Nasal Biomarker Sample

Nasal mucosal lining fluid (airway) sample from one nostril may be collected at the Randomization Visit and longitudinally as designated in the SoA. The same nostril should be used for subsequent collection, where possible. These samples may enable the evaluation of airway changes in the DP_2 pathway, Th2 pathway activity, and other markers that may correlate with biological response relating to CRS and/or the action of GB001. Sample collection should avoid use of local anesthetic and any anti-histamine use and should precede the Nasal Endoscopy (as indicated).

8.6.2. Blood Biomarker Analyses

Blood samples from peripheral vein(s) may be collected at the Randomization Visit and longitudinally as designated in SoA. These samples may enable the evaluation of peripheral changes in markers (eg, DP_2 pathway ligands, Th2 cytokines, and markers of granulocyte activation). For more details of the collection and processing of samples please refer to the Laboratory 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 CRS and/or the action of GB001. Samples will be collected at the clinic at baseline and at the end of the study. Samples are intended to be collected from all subjects but may not all be analyzed.

[redacted]

[redacted]

8.7. Pharmacogenetics

Single nucleotide polymorphisms may be analyzed as part of an exploratory PGx analysis, which may be performed on biosamples from subjects who have consented for this assessment and where permitted by local law. Subject confidentiality will be maintained, except under subpoena from regulatory and/or law enforcement agencies.

Samples may be collected from all subjects, except those who opt out and where impermissible by law and local authorities.

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 aims to demonstrate the superiority of GB001 versus placebo, when added to SOC therapy, on change from baseline to Week 16 in SNOT-22 score in the overall population and on change from baseline to Week 16 in NPS in the CRSwNP stratum.

9.2. Sample Size Determination

A total sample size of approximately 100 subjects overall (approximately 50 per treatment group, randomized in a 1:1 ratio) is estimated to provide approximately 90% power to detect a treatment difference of 12.0 between GB001 and placebo at a 0.050 two-sided level of significance for the primary endpoint of change from baseline to Week 16 in SNOT-22 score, assuming a common standard deviation of 16.8 and a dropout rate of 15% using a two-sided t-test.

A total sample size of approximately 64 subjects in the CRSwNP stratum (approximately 32 per treatment group, randomized in a 1:1 ratio) is estimated to provide approximately 80% power to detect a treatment difference of 1.3 between GB001 and placebo at a 0.050 two-sided level of significance for the secondary endpoint of change from baseline to Week 16 in NPS, assuming a common standard deviation of 1.7 and a dropout rate of 15% using a two-sided t-test.

Therefore, the total sample size of approximately 100 subjects overall will consist of approximately 64 subjects in the CRSwNP stratum and 36 subjects in the CRSsNP stratum.

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 used for summary of subject disposition.
- Run-in period population: All enrolled subjects who enter the Run-in period. This population will be used for summary of subject disposition.

- Intent-to-treat (ITT) population: All subjects who are randomized and receive at least one dose of IP, with subjects grouped according to randomized treatment. This population will be used for all efficacy analyses.
- Safety population: All subjects who receive at least 1 dose of IP, with subjects grouped according to their actual treatment. This population will be used for safety analyses.

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.

Analyses will generally be performed for the overall population and by stratum (CRSwNP and CRSsNP), other than endpoints associated with outcomes that are specific to the CRSwNP stratum (eg, NPS).

All statistical hypothesis testing will be at an 0.050 two-sided level of significance.

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analysis

The primary endpoint of change from baseline to Week 16 in SNOT-22 score will be analyzed by a mixed-effects model with repeated measures (MMRM) using a restricted maximum-likelihood (REML)-based approach. The MMRM model will include change from baseline scores up to Week 16 as the response variable; the fixed, categorical effects of treatment group, randomization strata defined by the presence or absence of NP and comorbid asthma (ie, CRSwNP with comorbid asthma, CRSwNP without comorbid asthma, and CRSsNP), country, visit, and treatment group by visit interaction; and the continuous, fixed covariates of baseline SNOT-22 score and baseline SNOT-22 score by visit interaction. An unstructured covariance structure will be used to model within-subject error. If this analysis fails to converge, a compound symmetric or first-order autoregressive covariance structure will be utilized for the primary analysis, based on the covariance structure converging to better fit as determined based on Akaike's information criterion.

Statistical inference for treatment group comparison of GB001 40 mg versus placebo at Week 16 will be derived from the above MMRM model, with results presented in terms of a least squares mean difference, along with the corresponding 95% confidence interval (CI) and p-value.

9.4.1.2. Secondary Efficacy Analysis

The secondary endpoints of change from baseline to Week 16 in Lund-Mackay total score and in UPSIT score will be analyzed utilizing analysis of covariance (ANCOVA) models including covariates for baseline score, presence or absence of bilateral NP, and treatment group. Results will be presented in terms of least squares mean differences, along with corresponding 95% CIs and p-values.

The secondary endpoints of change from baseline to Week 16 in NPS, NC, and TSS will be analyzed with MMRM using an REML approach, employing a similar methodological approach as the analysis of the primary endpoint. The analysis of change from baseline to Week 16 in NPS will be conducted in the CRSwNP stratum, with the fixed, categorical effect for randomization strata in the MMRM model defined by presence of NP and comorbid asthma (ie, CRSwNP with comorbid asthma and CRSwNP without comorbid asthma). For NC and TSS, the average of the scores recorded during the last 7 days before a given visit (14 scores, including the morning of the visit) will be used to determine the value for that visit.

The secondary endpoint of time to first response (≥ 1 point improvement from baseline) in NPS will be conducted in the CRSwNP stratum and will be analyzed using a stratified Cox proportional hazards model, stratified on the basis of the presence or absence of comorbid asthma, adjusted for country, baseline NPS, and treatment group. Subjects without a response in NPS will be censored at their last NPS assessment. The secondary endpoint of time to first CRS exacerbation will be analyzed using a stratified Cox proportional hazards model, stratified on the basis of the presence or absence of NP and comorbid asthma (ie, CRSwNP with comorbid asthma, CRSwNP without comorbid asthma, and CRSsNP), adjusted for country and treatment group. Subjects without a CRS exacerbation will be censored at their last assessment for CRS exacerbation. Kaplan-Meier estimates and curves will be provided for both time to first response in NPS and time to first CRS exacerbation.

9.4.2. Safety Analyses

Safety and tolerability will be examined based on AEs, clinical laboratory results, vital signs, and 12-lead ECG assessments.

Safety analyses will be focused on TEAEs, defined as AEs with onset on or after the first dose of IP. The incidence of AEs and SAEs will be summarized by treatment group, including the incidence by system organ class and preferred term. In addition, the incidence of AEs by severity, the incidence of treatment-related AEs, and the incidence of AEs leading to study drug discontinuation/study withdrawal will be summarized by system organ class and preferred term.

Laboratory, vital signs, and ECG data will be analyzed by treatment group using summary statistics for actual values of and change from baseline in 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 or high values based on normal ranges will also be presented.

9.5. Interim Analyses

No formal interim analyses are planned.

See Section 6.3.3 regarding unblinded analyses to be performed by Sponsor individuals not directly involved in the conduct of the study to inform further development of GB001.

10. APPENDICES

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations (site responsibilities)

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, IB, Diary 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 (or equivalent for non-IND sites), 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.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (or equivalent for non-IND sites), 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.
- Subjects 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.
- 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

- Subjects 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 (CSR) 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 3 and Table 4 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 3: Protocol-Required Safety Laboratory Assessments

Hematology	
White blood cell (WBC) count with differential (% and absolute for neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Red blood cell (RBC) with indices (mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]) and Mean Corpuscular Hemoglobin Concentration (MCHC)
Hemoglobin	Hematocrit
Platelet count	
Clinical Chemistry	
Liver Chemistries	
Alanine aminotransferase (ALT)	Aspartate aminotransferase (AST)
Alkaline phosphatase (ALP)[1]	Gamma-glutamyl transferase (GGT)
Total and direct bilirubin (fractionated)	Total bile acids
Albumin	Blood urea nitrogen (BUN)
Calcium	Chloride
Sodium	Creatinine
Glucose (non-fasting)	Potassium
Magnesium	Lactic dehydrogenase (LDH)
Uric acid	Total protein
Coagulation	
INR	
Urinalysis	
Basic Urinalysis (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen). Full urinalysis (dipstick plus microscopic evaluation) to be performed. 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 (FSH) and estradiol (as needed in women of non-childbearing potential only) • Viral hepatitis serology (hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)

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

The additional tests listed in Table 4 will be collected only if required as part of liver safety actions and follow up. See also Appendix 6 (Section 10.6).

Table 4: Liver Safety Laboratory Assessments

Hematology
Expanded viral hepatitis serology: • Hepatitis A immunoglobulin M (IgM) antibody • HBsAg and Hepatitis B core antibody (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 (refer to lab manual)
Chemistry
• Bile acids (bile acid, fractionated and total, liquid chromatography-tandem mass spectrometry (LC/MS-MS) if bile acid > 3 × ULN) • International normalized ratio (INR) • Serum creatine phosphokinase (CPK), also known as creatine kinase (CK) • 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, 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.

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
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 6) with the exception of events for which subjects cannot be monitored. Follow-up liver laboratory values (Table 4), 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, Table 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.

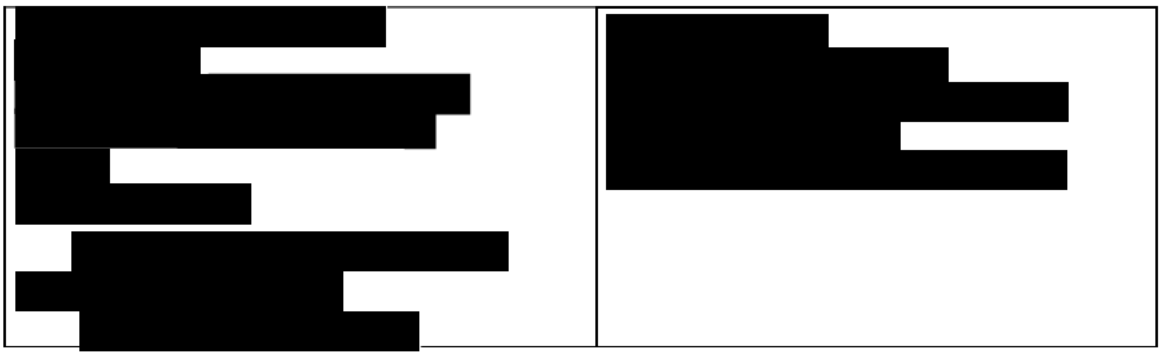
Follow-up of AEs and SAEs

- 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 if available.
- 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 below.



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 (eg, > 40 IU/L) 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:

- 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 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 – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

[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. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. 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 study intervention 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 may be collected for DNA analysis from consenting subjects.
- DNA samples may be used for research related to the relationship between safety, efficacy, and exposure parameters collected in this study, as they related to placebo, GB001, CRS, and related diseases. They may also be used to develop tests/assays including diagnostic tests related to GB001 and DP_2 inhibitors and/or atopic disease.
- Genetic research may consist of the analysis of candidate polymorphisms, prespecified in the statistical analysis plan.
- 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 a separate study summary.
- The Sponsor will store the 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.

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 5.

Table 5: 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 6 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 6), then follow the instructions in "Actions and Follow-up Assessments" in Table 6 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, the IP should be discontinued permanently.

The criteria requiring interruption of IP with additional liver monitoring is detailed in Table 6.

Table 6: Liver Chemistry Criteria Requiring Investigational Product Interruption and Additional Monitoring

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

Actions 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 > 2 × 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

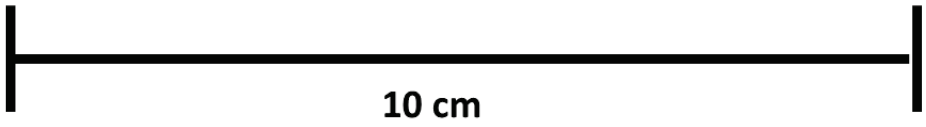
a. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue IP if ALT or AST ≥ 3 × ULN **and** bilirubin > 2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence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

b. All events of ALT or AST ≥ 3 × ULN **and** bilirubin > 2 × ULN (> 35% direct bilirubin) or ALT or AST ≥ 3 × ULN **and** INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to subjects receiving anticoagulants. INR is not part of routine laboratory assessments in this study.
c. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).
d. Includes: expanded viral hepatitis serology (Section 10.2 Table 4)

10.7. Appendix 7: Visual Analog scale (VAS)

To evaluate the total severity, the subject is asked to indicate on a VAS the answer to the question:

How troublesome are your symptoms of rhinosinusitis?



Not troublesome **Worst thinkable troublesome**

Example, not for use. Not to scale.

10.8. Appendix 8: ACQ-5 Questionnaire

The ACQ-5 questionnaire is located on the following page.

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

(SYMPTOMS ONLY)

For further information:

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Senior Translator:

DECEMBER 2002

ASTHMA CONTROL QUESTIONNAIRE©
(LANGUAGE VERSION FOR COUNTRY)

PATIENT ID: _____

DATE: _____

Please answer questions 1 - 5.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

5. In general, during the past week, how much of the time did you **wheeze**?
   - 0 Not at all
   - 1 Hardly any of the time
   - 2 A little of the time
   - 3 A moderate amount of the time
   - 4 A lot of the time
   - 5 Most of the time
   - 6 All the time

10.9. Appendix 9: SNOT-22 Questionnaire

The SNOT-22 questionnaire is located on the following page.

I.D.:_____ **SINO-NASAL OUTCOME TEST (SNOT-22)** DATE:_____

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Very Mild Problem	Mild or slight Problem	Moderate Problem	Severe Problem	Problem as bad as it can be		5 Most Important Items
1. Need to blow nose	0	1	2	3	4	5		O
2. Nasal blockage	0	1	2	3	4	5		O
3. Sneezing	0	1	2	3	4	5		O
4. Runny nose	0	1	2	3	4	5		O
5. Cough	0	1	2	3	4	5		O
6. Post-nasal discharge	0	1	2	3	4	5		O
7. Thick nasal discharge	0	1	2	3	4	5		O
8. Ear fullness	0	1	2	3	4	5		O
9. Dizziness	0	1	2	3	4	5		O
10. Ear pain	0	1	2	3	4	5		O
11. Facial pain/pressure	0	1	2	3	4	5		O
12. Decreased sense of smell/taste	0	1	2	3	4	5		O
13. Difficulty falling asleep	0	1	2	3	4	5		O
14. Wake up at night	0	1	2	3	4	5		O
15. Lack of a good night's sleep	0	1	2	3	4	5		O
16. Wake up tired	0	1	2	3	4	5		O
17. Fatigue	0	1	2	3	4	5		O
18. Reduced productivity	0	1	2	3	4	5		O
19. Reduced concentration	0	1	2	3	4	5		O
20. Frustrated/restless/irritable	0	1	2	3	4	5		O
21. Sad	0	1	2	3	4	5		O
22. Embarrassed	0	1	2	3	4	5		O

2. Please mark the most important items affecting your health (maximum of 5 items)_____ ↑

SNOT-22 Developed from modification of SNOT-20 by National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis Royal College of Surgeons of England.

10.10. Appendix 10: Prohibited and Restricted Medications and Treatments

Prohibited medications are defined as medications which require a washout prior to study entry (screening) or prior to randomization and are not permitted during the conduct of the trial. The following medications must be washed out for the period noted in Table 7 below and are prohibited throughout the study as they may interfere with endpoint interpretation.

Restricted medications are defined as medications which should be avoided, if possible; however, they are not prohibited during this study. If such medications are required, consider switching to another medication in the class that is not restricted (Table 8).

Table 7: Prohibited Medications and Treatments

Medication	Washout time from last dose prior to Screening visit
mepolizumab, reslizumab, benralizumab, omalizumab, dupilumab	5 half-lives (~4 months)
other nasal medications, such as oxymetazoline, azelastine, other INCS	5 half-lives
Immunosuppressive medications such as those listed below (not all inclusive)	
regular use of oral corticosteroids	1 month
nasal steroid drops, eluting stents (eg, Sinuva™)	1 month
intramuscular long-acting depot injections 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

Table 8: Restricted Medications Associated with an Increased Risk of Liver Injury

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.

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 (Table 9) and drink/food (Table 10) which may inhibit or induce CYP3A4 activities that will be prohibited 14 days prior to randomization through the safety Follow-up visit.

A non-exhaustive list of prohibited medications and drinks/food to prevent potential metabolic drug-drug interactions is incorporated into Table 9 and Table 10 and also will be provided in the Study Reference Manual.

Table 9: Prohibited Medications Associated with CYP3A4 Induction or Inhibition

Generic Name	Brand Name
amprenavir	Agenerase
aprepitant	Emend
armodafinil	Nuvigil
atazanavir	Reyataz
boceprevir	Victrelis
bosentan	Tracleer
carbamazepine	Tegretol, Biston, Calepsin, Carbatrol, Epitol, Equetro, Finlepsin, Sirtal, Stazepine, Telesmin, Teril, Timonil, Trimonil, Epimaz, and others
chloramphenicol	Chloramycetin
ciprofloxacin	Cipro, Cipro I.V., Cipro XR, Cipro Cystitis Pack
clarithromycin	Biaxin, Klaricid, Klabax, Claripen, Claridar, Fromilid, and others
conivaptan	Vaprisol
crizotinib	Xalkori
cyproterone	Androcur, Cyprostat, Cyproteron, Procur, Cyprone, Cyprohexal, Ciproterona, Cyproteronum, Neoproxil, Siterone
delavirdine	Rescriptor
dexamethasone	Decadron, Dexasone, Hexadrol
diethyl-dithiocarbamate	Disulfiram, Antabuse
dihydroergotamine	DHE 45
diltiazem	Cardizem, Tiazac, Dilacor, Cartia
efavirenz	Sustiva, Stocrin
ergotamine	Ergomar, Cafergot
erythromycin	Robimycin, Ery-Tab, EryPed, Erythrocin, and others
etravirine	Intelence
felbamate	Felbatol
fluconazole	Diflucan, Trican, and others
fosamprenavir	Lexiva

Table 9: Prohibited Medications Associated with CYP3A4 Induction or Inhibition (Continued)

Generic Name	Brand Name
gestodene	Femoden, Femodene, Femodette, Gynera, and others
dexamathasone	Decadron, Dexasone, Hexadrol
methylprednisolone	Medrol, Depo Medrol
prednisone	Deltasone, Rayos
prednisolone	Depo Medrol, Flo-Pred
griseofulvin	Grisovin
imatinib	Gleevec
indinavir	Crixivan
isavuconazole	Cresemba
isoniazid	Nydrazid
itraconazole	Sporanox
ketoconazole	Nizoral
lopinavir/ritonavir	Kaletra
mibefradil	Posicor
mifepristone	Mifeprex
modafinil	Provigil, Alertec, Modavigil
nafcillin	Unipen, Nallpen,Nafcil
nefazodone	Serzone, Nefadar
nelfinavir	Viracept
nevirapine	Viramune
oxcarbazepine	Trileptal
phenobarbital	Donnatal, Nembutal, and others
phenytoin	Phenytek, Dilantin, and others
fosphenytoin	Cerebyx, Prodilantin
posaconazole	Noxafil
primidone	Mysoline
quinupristin/dalfopristin	Synercid
rifabutin	Mycobutin

Table 9: Prohibited Medications Associated with CYP3A4 Induction or Inhibition (Continued)

Generic Name	Brand Name
rifampin	Rifidin, Rimactane
rifapentine	Priftin
ritonavir	Norvir
saquinavir	Invirase, Fortovase
telaprevir	Incivek
telithromycin	Ketek
tofisopam	Emandaxin, Grandaxin

Table 10: Prohibited Food and Herbal Supplements Associated with CYP3A4 Induction or Inhibition

Name	Brand Names	Notes/Description
Grapefruit /Grapefruit juice		Includes sodas that contain concentrated grapefruit juice
Marmalade		
Seville/blood oranges		
St. John's Wort		
Curcumin		

10.11. Appendix 11: 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 GB001-2101 protocol may be made as described below, in line with global regulatory authorities guidance in order to ensure the safety of study participants, maintain compliance with GCP, and minimize the risks to 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 the SNOT-22 questionnaire in order to assess subject status.
  - The subject should continue to collect the daily morning and evening symptom diary as described in Section 8.1.4.
- Alternative methods of collecting study assessments may be considered where possible:
  - Questionnaires, including SNOT-22, UPSIT, and ACQ-5, 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.

10.12. Appendix 12: Abbreviations

Abbreviation Term	Description
ACQ-5	Asthma Control Questionnaire
AE	adverse event
AERD	aspirin-exacerbated respiratory disease
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
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
COX-2	cyclooxygenase 2
CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
CSR	clinical study report
CT	Computed Tomography
CTFG	Clinical Trial Facilitation Group
CysLT	cysteinyl leukotriene
DILI	drug induced liver injury
DP_2	prostaglandin D_2 receptor
ECG	electrocardiogram
ECP	eosinophil cationic protein
eCRF	electronic case report form
eCRS	eosinophilic chronic rhinosinusitis
EW	early withdrawal
FeNO	fractional exhaled nitric oxide
FEV1	forced expiratory volume in 1 second

Abbreviation Term	Description
FSH	follicle-stimulating hormone
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
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IL	interleukin (IL-4, IL-5, IL-13)
ILC2	Group 2 innate lymphoid cells
INCS	intranasal corticosteroids
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhoea method
LDH	lactate dehydrogenase
LXA4	lipoxin A4
MCID	minimal clinically important difference
MFNS	mometasone furoate nasal spray

Abbreviation Term	Description
MMRM	mixed-effects model with repeated measures
NAFLD	non-alcoholic fatty liver disease
NC	nasal congestion
nNO	nasal nitric oxide
NP	nasal polyps
NPS	nasal polyp score
OC	osteomeatal complex
PD	pharmacodynamic
PGD_2	prostaglandin D_2
PGE_2	prostaglandin E2
PGx	pharmacogenetics
PK	pharmacokinetic
QD	once daily
QTcF	Fridericia's correction formula for QT interval (interval between Q wave and T wave)
RBC	red blood cell
REML	restricted maximum-likelihood
RNA	ribonucleic acid
SAE	serious adverse event
SNOT-22	Sino-Nasal Outcome Test
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
TSS	total symptom score
ULN	upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test
VAS	visual analog scale
WBC	white blood cell
WOCBP	women of childbearing potential

10.13. Appendix 13: 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 4 (v4.0)	18 Feb 2020
Amendment 3 (v3.0)	28 Aug 2019
Amendment 2 (v2.1)	02 May 2019
Amendment 1 (v2.0.0)	05 Apr 2019
Original Protocol (v1.0.0)	24 Jan 2019

Amendment 4 (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 primary purpose of this amendment is to enhance monitoring of liver parameters during the conduct of the trial and provide clarification on eligibility criteria.

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 following Randomization (Visit 2). Added CRS exacerbation review at Visits 1, 2, and 2.5.	Week 1 visit was added to enhance laboratory monitoring during the first month following IP initiation. Clarified that CRS exacerbation review is performed at every visit.
Section 4.1.1 Study Design; Section 4.2.1 Study Population; Section 6.3.1 Randomization	Added visual examination as a method of confirming absence of nasal polyps	Clarified definition of absence of nasal polyps
Section 5.3 Randomization Criteria #6	Modification of the randomization criteria from ALT and AST $< 2 \times$ ULN to ALT and AST $\leq 1 \times$ ULN	Enhance safety characterization of the study population
Section 6.3.4 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 # and Name	Description of Change	Brief Rationale
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 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	To enhance monitoring of liver parameters during the conduct of the trial
Global Change	Minor revisions to text	Administrative updates were incorporated, and typographical errors were corrected

Amendment 3 (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.

Overall Rationale for the Amendment:

The primary 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 and provide clarification on eligibility criteria.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities; Section 1.2 Schema	• Notes on total bile acid, international normalized ratio (INR), and fractionation of ALP if ALP > 1xULN were added. • Added assessment of clinical chemistry at Week 3. • Added separate line for concomitant medications.	• Addition of INR measurement at baseline. Collection of 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. • Clarified timing of concomitant medications.
Section 2.3.1 GB001 Risk/Benefit Assessment	Revised data for GB001.	Clarified risk/benefit profile.
Section 5.1 Inclusion Criterion #2	Maximum age was increased.	Higher maximum age allowed because no additional risk is expected in this extended population.
Section 5.2 Exclusion Criteria #2	Clarified polypectomy performed as an outpatient procedure will not exclude subject from study.	Polypectomy performed as an outpatient procedure is considered a minor surgery.
Section 5.2 Exclusion Criteria #5	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 #2	Updated nasal polyp score (NPS) range for exclusion from randomization.	Clarified that subjects with NPS of 0 are eligible for randomization.
Section 5.3 Randomization Criteria #6	Added maximum absolute eosinophil count and white blood cell (WBC) count criteria.	Enhance safety characterization of the study population
Section 6.5.1 Prohibited Medications Prior to the Screening Visit and Throughout the Study;	• Added the concept of restricted medications. Referred investigators to list of medications in Appendix 10 which include those	• Increased awareness of medications which may impact liver effects and those drugs/agents that may inhibit or induce CYP3A.

Section # and Name	Description of Change	Brief Rationale
Section 10.10 Appendix 10: Prohibited Medications and Treatments	medications known to have the potential for drug induced liver injury (DILI) as well as CYP3A inhibitors and inducers. • Removed XHANCE™ as a prohibited medication.	• Intranasal corticosteroid delivered via a specialized device will be allowed under Inclusion Criteria #6.
Section 8 Study Assessments and Procedures	Added language on nasal endoscopy and nitric oxide measurement at Randomization visit.	Clarified which subjects should receive nasal endoscopy and that all subjects should have nitric oxide measurement.
Section 8.1.2 Computed Tomography (CT)	Updated language that prior CT may be acceptable under specific conditions.	Clarification that a prior CT within 60 days of the Randomization visit of satisfactory quality may be acceptable.
Section 10.2 Appendix 2: Clinical Laboratory Tests Table 3	Total bile acid, INR, and fractionation of ALP if ALP > 1xULN were added.	To enhance monitoring of liver parameters during the conduct of the trial.
Global Change	Minor revisions to text.	Administrative updates were incorporated, and typographical errors were corrected.

Amendment 2 (v2.1; 02 May 2019)

This amendment is considered to be nonsubstantial 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 because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to remove assessment of nitric oxide at the Screening visit.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Removed assessment of nitric oxide at Screening visit.	Nasal nitric oxide (nNO) and fractional exhaled nitric oxide (FeNO) tests are not required at the time of screening.
Section 2.2 Background	Added results from a recent poster.	Updated with results which suggest that GB001 influences lung function in subjects with markers of eosinophilic inflammation.
Section 7.1 Discontinuation of Investigational Product	Included separate section on liver safety.	Clarification on liver chemistry criteria that will result in permanent discontinuation of investigational product.
Section 8.1.2 Computed Tomography (CT)	Updated text to imaging core laboratory.	Clarification that imaging core laboratory will analyze CT sequences.
Section 10.3.5 Reporting of SAEs	Contact information was updated.	Updated contact information for sites outside North America.
Global Change	Minor revisions to text.	Administrative updates were incorporated, and typographical errors were corrected.

Amendment 1 (v2.0.0; 5 Apr 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 primary purpose of this amendment is to increase the sample size of the study, include an exclusion criterion for AERD, incorporate additional objectives and endpoints, and revise the statistical considerations section to reflect the increased sample size and additional endpoints.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis; Section 1.2 Schema; Section 4.1.1 Study Design; Section 4.2.1 Study Population; Section 6.3.1 Randomization; Section 9 Statistical Considerations	Total sample size increased to 100. Added text on randomization and stratification.	Increased total number of subjects by 30 to enable better characterization of benefit-risk profile in subjects with nasal polyps. Clarification on randomization and stratification.
Section 1.1 Synopsis; Section 1.3 Schedule of Activities; Section 3 Objectives and Endpoints; Section 8.1.9 Other Assessments; Section 9.4.1.2 Secondary Efficacy Analysis	Included additional secondary endpoint and clarified previous endpoints.	Added and clarified secondary endpoints to evaluate data including exacerbations, time to first response in NPS, and change in total symptom score to better characterize CRS.
Section 1.3 Schedule of Activities	Hepatitis B surface antigen and Hepatitis C antibody text was updated.	Clarification to include indeterminate test result.
Section 1.3 Schedule of Activities; Section 4.1.1 Study Design; Section 4.2.1 Study Population; Section 5.3 Randomization Criteria; Section 8 Study Assessments and Procedures	Added use of mometasone furoate nasal spray (MFNS) equivalent.	MFNS may not be available in some ex-US countries and therefore an equivalent product may be used.
Section 3 Objectives and Endpoints	Included additional exploratory endpoints.	Added 3 exploratory endpoints to further understand the role of GB001 in CRS.
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

Section # and Name	Description of Change	Brief Rationale
		obtaining historical medical records when necessary.
Section 4.2.1 Study Population; Section 5.2 Exclusion Criteria	Add aspirin-exacerbated respiratory disease (AERD) exclusion criterion.	Remove subjects with AERD to maintain a more homogeneous study population.
Section 5.2 Exclusion Criteria	Text around ECG assessment was updated.	This modification was made to improve clarity that ECG assessment could be repeated.
Section 5.2 Exclusion Criteria	Text was added to exclude smoking of any substance.	This clarification was made to include marijuana, its components, and any other substances which may be smoked.
Section 5.3 Randomization Criteria; Section 8 Study Assessments and Procedures; Section 8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	Added criterion for subjects who experience an exacerbation. Added definition of an exacerbation and clarification regarding adverse event qualification.	Clarification on timing of randomization for subjects who experience an exacerbation. Definition was added to characterize worsening of disease (exacerbations) that may occur during the 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 6.3.3 Unblinding of an Individual Subject; Section 9.5 Interim Analyses	Text added to clarify conditions for unblinding.	Clarification of procedures to protect samples and data for unblinding.
Section 7.1.1 Pregnancy	Updated 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	Changed order of assessments	Arranged assessments such that efficacy assessments follow the ordering of endpoints.
Section 8.6.3 RNA Transcriptome Research	Text was updated.	Clarification that not all samples may be analyzed.

Section # and Name	Description of Change	Brief Rationale
Section 10.10 Appendix 10: Prohibited Medications and Treatments	Clarification in reference to a medication.	Replaced company name (Optinose) with trade name (XHANCE).
Global Change	Minor revisions to text.	Typographical errors were corrected.

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