Protocol

GB1211 - A Randomised, Double-Blind, Placebo-Controlled, First-In-Human, Study of Orally Administered GB1211 to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses (SAD) and Multiple Ascending Doses (MAD) in Healthy Subjects and in Subjects with Suspected Nonalcoholic Steatohepatitis (NASH) and Liver Fibrosis

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Sponsor:
Galecto Biotech
Cobis Science Park
Ole Maaloes Vej 3
DK-2200 Copenhagen
Denmark

Sponsor Signatory: [redacted]

Principal Investigator: [redacted]

SPONSOR APPROVAL

I have read the protocol and approve it:

[redacted]

[redacted]

Chief Medical Officer, Galecto Biotech

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

[redacted] [redacted]

[redacted] Date

Principal Investigator

SUMMARY OF AMENDED PROTOCOL CHANGES

PROTOCOL VERSION 2.0 (AMENDMENT 1)

This amendment to the Final Study Protocol, dated 11 October 2018, has been issued to add a study restriction to minimise exposure to ultraviolet (UV) light as recommended by the Medicines and Healthcare products Regulatory Agency (MHRA).

Details of the changes incorporated in this amendment are provided in the table below.

Protocol Section	Description of Changes from Final Protocol, dated 11 October 2018
1.5	New text added in **bold**: **In albino and pigmented mice,** [^{14}C]-GB1211-related radioactivity was well absorbed and rapidly distributed into tissues, [^{14}C]-GB1211-related radioactivity was rapidly eliminated from tissues, and the mean overall recovery of the radioactivity administered was 103%. **GB1211 showed a trend for distribution to the uveal tract and skin of pigmented mice. This was reversible and below the limit of quantification at 168 hours.**
4.4	Addition of exclusion criterion 20: **Subject is not willing to minimise or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) following administration of study drug until 24 hours after the last dose**.
4.5	Addition of exclusion criterion 20: **Subject is not willing to minimise or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) following administration of study drug until 24 hours after the last dose.**
4.6	Addition of exclusion criterion 26: **Subject is not willing to minimise or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) following administration of study drug until 24 hours after the last dose.**
6.6	An additional section was added to Section 6:

	6.6. Exposure to Ultraviolet Light **Subjects should minimise or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) following administration of study drug until 24 hours after the last dose. If subjects need to be outdoors during this period, they should wear loose fitting clothes that protect skin from sun exposure and discuss other sun protection measures with the Investigator.**

STUDY IDENTIFICATION

Sponsor	Galecto Biotech Cobis Science Park Ole Maaloes Vej 3 DK-2200 Copenhagen Denmark
Sponsor's Study Contact	[redacted] Chief Medical Officer Galecto Biotech Cobis Science Park Ole Maaloes Vej 3 DK-2200 Copenhagen Denmark
Medical Monitor	[redacted] Covance Maidenhead Office Park Westacott Way Littlewick Green Maidenhead, SL6 3QH UK [redacted]
Study Site (Parts A and B)	Covance Clinical Research Unit Ltd. Springfield House Hyde Street Leeds, LS2 9LH UK
Part C Study Site(s) and Investigator(s)	Study site(s) and Investigator(s) in the EU
Principal Investigator (Parts A and B)	[redacted] Covance Clinical Research Unit Ltd. Springfield House Hyde Street Leeds, LS2 9LH UK [redacted]
Clinical Laboratory (Parts A and B)	Covance Clinical Pathology Services Otley Road Harrogate, HG3 1PY UK
Bioanalytical Laboratory	Covance Laboratories Ltd

	Otley Road Harrogate, HG3 1PY UK
Statistician	[redacted] Covance Biometrics

SYNOPSIS

Title of study: GB1211 – A Randomised, Double-Blind, Placebo-Controlled, First-In-Human, Study of Orally Administered GB1211 to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses (SAD) and Multiple Ascending Doses (MAD) in Healthy Subjects and in Subjects with Suspected Nonalcoholic Steatohepatitis (NASH) and Liver Fibrosis

Objectives:

The primary objectives of the study are:

- to evaluate the safety and tolerability of single and multiple doses of GB1211 administered to healthy subjects.
- to evaluate the safety and tolerability of multiple doses of GB1211 administered to subjects with suspected NASH and liver fibrosis.

The secondary objectives of the study are:

- to evaluate the pharmacokinetics (PK) of single doses of GB1211 in plasma and urine in healthy subjects, and the PK of multiple doses of GB1211 in plasma of healthy subjects and subjects with suspected NASH and liver fibrosis
- to determine the effect of food on the single oral dose PK of GB1211.

The exploratory objectives of the study are:

- to investigate biomarkers related to GB1211 activity at single and/or multiple doses in comparison to placebo in healthy subjects and subjects with suspected NASH and liver fibrosis.
- to investigate biomarkers of metabolism, inflammation, and fibrosis following multiple doses of GB1211 in healthy subjects and/or subjects with suspected NASH and liver fibrosis.
- to identify metabolites of GB1211 in plasma and urine.

Study design:

This is a Phase 1, randomised, double-blind, placebo-controlled, first-in-human study in which the safety, tolerability, and PK of orally administered GB1211 will be assessed in healthy adult subjects and adult subjects with suspected NASH and liver fibrosis.

Suspected NASH is defined as the presence or history of fatty liver, together with elevated alanine aminotransferase (ALT), plus either confirmed type 2 diabetes mellitus (T2DM) or metabolic syndrome, in the absence of any other liver disease. Additional criteria aim to enrich for individuals with liver fibrosis (as per inclusion criteria).

The study will consist of 3 parts: a SAD phase (Part A) enrolling a total of 5 cohorts of healthy subjects; a MAD phase (Part B) enrolling 2 cohorts of healthy subjects; and an optional Part C MAD phase enrolling 1 cohort of subjects with suspected NASH and liver fibrosis. One cohort of Part A will receive GB1211 under both fasted and fed conditions to investigate the effect of food.

Number of subjects:

Part A: 40 subjects will be studied in 5 cohorts (Cohorts A1 to A5)
Part B: 22 subjects will be studied in 2 cohorts (Cohorts B1 to B2)
Part C: 25 subjects will be studied in 1 cohort (Cohort C1)

Diagnosis and main criteria for inclusion:
Parts A and B:
Male or female subjects aged between 18 and 55 years (inclusive) for Part A, and between 18 and 60 years (inclusive) for Part B; with a body mass index (BMI) ≥ 18.0 kg/m^2 and ≤ 32.0 kg/m^2, who must be healthy, as determined by no clinically significant findings from medical history, physical examination, 12-lead electrocardiogram (ECG), vital signs measurements, and clinical laboratory evaluations (congenital nonhaemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening and Check-in as assessed by the Investigator (or designee), as applicable.
Part C:
Male or female subjects aged between 18 and 60 years (inclusive) with a BMI ≥ 25.0 kg/m^2 and ≤ 38.0 kg/m^2 and a documented history of fatty liver within the last 24 weeks by one of the following: magnetic resonance imaging (MRI) suggesting liver fat ≥ 8%, ultrasound (US) indicating fatty liver, or Fibroscan Controlled Attenuation Parameter (CAP) > 270 dB/m. In subjects without a documented history of fatty liver, a Fibroscan CAP or US can be performed at Screening. Subjects with a Fibroscan CAP > 270 dB/m or US indicating fatty liver are eligible. In addition, subjects should have metabolic syndrome (Adult Treatment Panel III definition) or T2DM (defined as stable diabetes with glycosylated haemoglobin (HbA1c) ≤ 9.5%); have ALT ≥ 20 U/L for females and ≥ 30 U/L for males at Screening; and have Fibroscan ≥ 7 KPa and < 13 KPa, or Fibrosis-4 (FIB-4) index ≥ 1.1 and < 3.25.

Investigational products, dose, and mode of administration:
Test products: 5 and 50 mg GB1211 capsules
Proposed dose levels for Part A: 5, 20, 50, 100, and 200 mg
Proposed dose levels for Part B: to be determined based on data from Part A.
Proposed dose level for Part C: to be determined based on data from Part A, and data from at least 1 Part B cohort.
The dosing frequency/interval and dosing duration for Part B will be fully decided, in consultation with the Sponsor, on the basis of data from Part A; and for Part C, will be fully decided on the basis of data from Part A and at least 1 Part B cohort. The daily dose administered will not exceed the highest dose administered in Part A.
Administration route: oral

Reference product and mode of administration:
Reference product: placebo capsules
Administration route: oral

Duration of subject participation in the study:
Planned Screening duration: approximately 4 weeks.
Planned study duration (Screening to Follow-up):
Part A, Cohorts A1 to A5 (excluding food-effect cohort, planned to be Cohort A3: approximately 5 weeks.
Part A, Food-effect cohort (planned to be Cohort A3): approximately 6 to 7 weeks.
Part B: approximately 6 to 7 weeks.
Part C: approximately 11 weeks.

Endpoints:

Primary endpoints:

Incidence and severity of adverse events, incidence of laboratory abnormalities (haematology, clinical chemistry, urinalysis), 12-lead ECG parameters, vital signs measurements, and physical examinations.

Secondary endpoints:

Blood samples for the analysis of plasma concentrations of GB1211 following single and multiple oral doses of GB1211. In addition, urine samples for the analysis of urinary concentrations of GB1211 following single oral doses of GB1211 (Part A).

The PK parameter endpoints for Part A will include area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$), maximum observed plasma concentration (C_{max}), time of the maximum observed plasma concentration (T_{max}), apparent plasma terminal elimination half-life ($t_{1/2}$), apparent total plasma clearance (CL/F), apparent volume of distribution (V_z/F), amount of drug excreted in urine (A_e), percentage of dose excreted unchanged (f_e) in urine, and renal clearance (CL_R). In Parts B and C, the PK parameters will include AUC over a dosing interval ($AUC_{0-\tau}$), $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, minimum observed plasma concentration (C_{min}), observed accumulation ratio based on $AUC_{0-\tau}$ ($RA_{AUC0-\tau}$), and observed accumulation ratio based on C_{max} (RA_{Cmax}). Other PK parameters may also be reported.

Exploratory endpoints:

For all SAD and MAD cohorts (Parts A, B, and C), exploratory biomarker endpoints include serum galectin-3, chemokine (C-C motif) ligand (CCL)-4 (CCL4), and other biomarkers may also be measured in an exploratory fashion. For all MAD cohorts (Parts B and C), changes from baseline at Day 10 (healthy subjects) and Day 42 (subjects with suspected NASH and liver fibrosis) will be assessed in fasting plasma glucose and insulin; in lipid profile; in heat shock C-reactive protein (hsCRP), interleukin (IL)-12, monocyte chemotactic protein (MCP)-1, tumor necrosis factor (TNF)-alpha, CCL2, CCL3, CCL4 and the chemokine (C-C motif) receptors (CCR)-1 and CCR2; and other biomarkers of inflammation as required. For the MAD cohort in subjects with suspected NASH and liver fibrosis (Part C), changes from baseline at Day 42 in biomarkers of fibrosis, including but not limited to extracellular matrix proteins (tissue inhibitor of matrix metalloproteinase-1 [TIMP-1], hyaluronic acid [HA], and aminoterminal peptide of pro-collagen III [P3NP]), A9, E74-like transcription factor (ELF) panel, cytokeratin (CK)-18, plasminogen activator inhibitor (PAI)-1, chitinase-3-like protein-1 (CH3L1), IL6, and pro-collagen 3. In addition, identification of GB1211 metabolites in plasma and urine.

Statistical methods:

Pharmacokinetics:

Individual plasma and urine concentrations of GB1211 (Part A only for urine concentrations) will be listed and summarised using descriptive statistics. Individual and mean GB1211 concentration-time profiles will be presented graphically.

Where data are available, GB1211 dose proportionality will be examined across the dose cohorts. The PK parameters will be analysed for dose proportionality using a power model approach or analysis of variance (ANOVA) model as appropriate. Where data are available, the effect of food at 1 dose level in Part A will be investigated using an ANOVA model.

Exploratory biomarker data:

Exploratory biomarker data will be listed and summarised using descriptive statistics. No formal statistical analysis of exploratory biomarker data is planned.

Safety:

Safety parameters will be listed and summarised using descriptive statistics. No formal statistical analysis of safety data is planned.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
A_e	amount of drug excreted in urine
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24 hours postdose
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
$AUC_{0-tlast}$	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
$AUC_{0-\tau}$	area under the plasma concentration-time curve over a dosing interval
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
CAP	Controlled Attenuation Parameter
CCL	chemokine (C-C motif) ligand
CCR	chemokine (C-C motif) receptor
CFR	Code of Federal Regulations
CH3L1	chitinase-3 like protein-1
CK18	cytokeratin 18
CL/F	apparent total plasma clearance
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CRO	Contract Research Organisation
CRU	Clinical Research Unit
CSA	clinical study agreement
CYP	cytochrome P450
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
ELF	E74-like transcription factors
eCRF	electronic Case Report Form

EDC	electronic data capture
ELF	E74-like transcription factors
f_e	percentage of drug excreted unchanged
FIB-4	Fibrosis-4
FL	fatty liver
FSH	follicle-stimulating hormone
GLP	Good Laboratory Practice
HA	hyaluronic acid
HbA1c	glycosylated haemoglobin
HDL	high density lipoprotein
HED	human equivalent dose
hERG	human ether-à-go-go-related gene
hsCRP	heat shock C-reactive protein
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IL	interleukin
IMP	investigational medicinal product
LBBB	left bundle branch block
LDL	low density lipoprotein
MAD	multiple ascending dose(s)
MCP-1	monocyte chemotactic protein-1
MHRA	Medicines and Healthcare products Regulatory Agency
MRSD	maximum recommended starting dose
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NOAEL	no observed adverse effect level
P3NP	aminoterminal peptide of pro-collagen III
PAI-1	plasminogen activator inhibitor-1
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
$RA_{AUC0-\tau}$	observed accumulation ratio based on $AUC_{0-\tau}$
RA_{Cmax}	observed accumulation ratio based on C_{max}

SAD	single ascending dose(s)
SAE	serious adverse event
$t_{1/2}$	apparent plasma terminal elimination half-life
T2DM	type 2 diabetes mellitus
TBD	to be determined
TIMP-1	tissue inhibitor of matrix metalloproteinase-1
T_{max}	time of the maximum observed plasma concentration
TMF	Trial Master File
TNF-α	tumor necrosis factor-α
ULN	upper limit of normal
US	ultrasound
UV	ultraviolet
V_z/F	apparent volume of distribution
WBC	White blood

1. INTRODUCTION

1.1. Overview

Galectin-3, a beta-galactoside binding lectin, is a key regulator of fibrosis and inflammation in lung, liver, and kidney. Mice deficient in galectin-3 are protected from fibrosis and exhibit reduced scarring in response to injury. Galectin-3 regulates myofibroblast differentiation (the major source of collagens during tissue fibrosis) and also has profound effects on macrophage polarisation. In addition, secretion of galectin-3 by macrophages results in activation of myofibroblasts, further amplifying a pro-fibrotic loop.[1,2] Galectin-3 inhibitors, when delivered locally in the lung, have also been shown to reduce fibrosis in mice.[3,4]

Nonalcoholic fatty liver disease (NAFLD) affects about a third of the adult population in Western nations, and may manifest histologically as a fatty liver or steatohepatitis. Fatty liver is generally non-progressive or progresses slowly compared to nonalcoholic steatohepatitis (NASH), which is more likely to lead to progressive fibrotic remodelling of the liver culminating in cirrhosis. Prevalence of NASH cirrhosis is growing and it is at present, the second leading cause for liver transplantation. There is no approved therapy for NASH or NASH fibrosis.

The gold standard methodology for the diagnosis on NASH is liver biopsy. Nonalcoholic steatohepatitis is characterised by a pattern of injury composed of steatosis, lobular inflammation, and ballooning degeneration. Liver biopsy is an invasive methodology and subject to a certain degree of sampling variability; however, there are no noninvasive tools to diagnose definite NASH with enough accuracy to serve as a stand-alone entry criteria for advanced phase trials and to avoid using histology-based endpoints. However, in early proof of concept trials, noninvasive models are generally used to identify those who may have definite NASH with some degree of fibrosis ("suspected NASH with liver fibrosis").[5]

Galecto Biotech is developing a systemically active galectin-3 inhibitor for the treatment of fibrotic disorders such as NASH, renal fibrosis, and cardiac fibrosis. This is the first time GB1211 will be administered to humans. Additional details on GB1211 can be found in the Investigator's Brochure (IB).[6]

1.2. Summary of Nonclinical Pharmacology

In 2 primary pharmacodynamic (PD) studies, the effect of GB1211 on carbon tetrachloride-induced liver fibrosis in mice was evaluated. The percentage area of Picrosirius Red positive staining in liver sections was significantly reduced in animals given 10 mg/kg GB1211 twice daily (BID; $p = 0.009$), indicating decreased fibrotic collagen deposition in the hepatic parenchyma; and significantly reduced ($p \leq 0.05$) in once daily and BID groups in a second study. The collagen content, measured by hydroxyproline, was also found to be significantly reduced in the BID group of one study. There were no clear significant changes in liver function, liver fibrosis biomarkers, or indicators of the collagen life cycle, with the exception of increased serum ALT with 10 mg/kg GB1211 BID in 1 study. In a secondary PD study, GB1211 showed no cross-reactivity against an industry standard panel of 87 enzyme and radioligand binding assays.

1.3. Summary of Safety Pharmacology

In a Good Laboratory Practice (GLP) study in male CD-1 mice, no effects were observed on the central nervous system or body temperature or respiratory parameters when given a single oral dose of up to 500 mg/kg. In another GLP study in male telemeterized Beagle dogs, no effects were observed on hemodynamic or electrocardiography parameters, or body temperature, when given a single oral dose of up to 50 mg/kg. In 6-week repeat-dose toxicity studies, there was also no evidence of gastrointestinal toxicity or renal toxicity in mice or dogs; and GB1211 was negative in all genotoxicity studies.

In addition, 2 human ether-à-go-go-related gene (hERG) studies were conducted. In the non-GLP study, GB1211 significantly ($p \leq 0.05$) inhibited the hERG tail current density at 1 and 10 µM by 16.8% and 35.9%, respectively. There was no evidence of reversal based on measures taken after a 5-minute washout period in cells exposed to 10 µM. In the GLP study, GB1211 significantly ($p < 0.05$) inhibited the hERG tail current amplitude at all concentrations (6.83%, 28.51%, 57.60%, and 93.33% for 0.3, 1, 10, and 100 µM, respectively). The half maximal inhibitory concentration (IC_{50}) was 5.06 µM (2700 ng/mL).

1.4. Summary of Toxicology

As detailed in Section 4.3 of the IB[6], repeat-dose toxicity studies were conducted in 2 species, the CD-1 mouse and Beagle dog:

- In 2 mice repeat-dose toxicity studies, there were no GB1211-related deaths.
    - In a non-GLP study, there were no significant findings in mice given single escalating oral doses up to 500 mg/kg, or daily oral doses at 500 mg/kg/day for 14 days. No effects on body weights, food consumption, clinical pathology, organ weights, or macroscopic or microscopic findings were observed. Systemic saturation was observed at doses > 50 mg/kg/day.
    - In the 6-week GLP study (doses of 50, 150, and 500 mg/kg/day), there were no GB1211-related deaths. However, there were 10 deaths in total, with 4 animals sacrificed in moribund condition with eye-related changes, 3 were due to gavage errors (2 were sacrificed moribund, 1 was found dead), and the cause of 3 deaths was not determined (1 was sacrificed moribund due to clinical observations and 2 were found dead). Additional details for these deaths can be found in the IB[6] (Section 4.3.2.1.2). No GB1211-related, adverse effects were observed (no effects on clinical signs, ophthalmic observations, body weights, food consumption, clinical pathology parameters, organ weight, or macroscopic or microscopic pathology were observed in the dosing or recovery periods). The no observed adverse effect level (NOAEL) was 500 mg/kg/day, which corresponded to maximum observed plasma concentration (C_{max}) values of 17005.0 and 22506.6 ng/mL, and area under the plasma concentration-time curve (AUC) from zero to the time of the last quantifiable concentration ($AUC_{0\text{-tlast}}$) values of 46617.4 and 58355.9 ng·h/mL, for males and females, respectively, on Day 42 (Table 1).

- In 2 dog repeat-dose toxicity studies, systemic saturation was observed at doses > 50 mg/kg. No GB1211-related adverse effects were observed. Increases in QT and QT interval corrected for heart rate (QTc) intervals noted in males at 15 or 50 mg/kg/day and females at 50 mg/kg/day were not considered adverse because the range of individual QT values were within what would be considered the normal range for the dog. The left bundle branch block (LBBB) noted in one female at 50 mg/kg/day (1 hour postdose in Week 6) is not a normal variation in dogs, however, as it was present during the predose phase collection for this animal, it was not considered to be GB1211 related (*Covance study 8377741 – to be published*). In addition, no electrocardiogram (ECG) findings were observed in telemeterized dogs given up to 50 mg/kg in the cardiovascular safety pharmacology study. The NOAEL was 50 mg/kg/day, which corresponded to C_{max} values of 27047.0 and 17789.9 ng/mL, and $AUC_{0\text{-tlast}}$ values of 117585.2 and 63452.2 ng·h/mL, for males and females, respectively, on Day 42 (Table 2).

In addition, there was no genotoxic potential for GB1211 in appropriately conducted assays in bacteria (reverse mutation test), human lymphocytes (in vitro micronucleus test), and in mouse bone marrow (in vivo micronucleus test).

No developmental and reproductive toxicology studies have been conducted so far.

1.5. Summary of Nonclinical Pharmacokinetics

In the 6-week GLP study[6] in CD-1 mice (doses of 50, 150, and 500 mg/kg/day; Table 1) C_{max} values were reached between 15 minutes and 2 hours. Apparent plasma terminal half-life ($t_{1/2}$) values ranged between 1.93 and 3.63 hours. In general, increases in $AUC_{0\text{-tlast}}$ on Day 1 and Day 42 were less than dose-proportional between 50 and 500 mg/kg, with $AUC_{0\text{-tlast}}$ being higher at 150 mg/kg/day than at 500 mg/kg/day on Day 42 for both male and females.

The C_{max} and $AUC_{0\text{-tlast}}$ values on Day 42 decreased after daily administration. No sex differences were observed.

Table 1: Pharmacokinetics Parameters of GB1211 in Mice

Day	Dose (mg/kg/day)	Sex	$AUC_{0\text{-tlast}}$ (ng.h/mL)	C_{max} (ng/mL)	T_{max} (h)
1	50	male	85188.1	25548.7	0.50
		female	58347.7	14780.3	0.50
	150	male	86490.1	38013.2	0.25
		female	90348.9	38686.2	0.25
	500	male	95727.5	41296.0	0.25
		female	71134.5	40542.6	0.25
42	50	male	41631.3	12156.1	1.00
		female	46117.4	9952.2	2.00
	150	male	52541.3	17555.2	1.00
		female	61185.3	21443.2	1.00
	500[a]	male	46617.4	17005.0	0.25
		female	58355.9	22506.6	0.25

Abbreviations: $AUC_{0\text{-tlast}}$ = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; C_{max} = maximum concentration; T_{max} = time to maximum concentration.
[a] The no observed adverse effect level

In the 6-week study in Beagle dogs[6] (doses of 5, 15, and 50 mg/kg/day; Table 2) C_{max} values were reached between 0.5 and 1.02 hours. Values for $t_{1/2}$ ranged between 4.47 and 8.23 hours. In general, increases in $AUC_{0\text{-tlast}}$ values on Day 1 and Day 42 were approximately dose-proportional between 5 and 15 mg/kg and were less than dose-proportional between 15 and 50 mg/kg. Mean C_{max} and $AUC_{0\text{-tlast}}$ values were similar between Day 1 and Day 42, suggesting no accumulation. Concentrations were generally higher for males when compared to females.

Table 2: Pharmacokinetics Parameters of GB1211 in Beagle Dogs

Day	Dose (mg/kg/day)	Sex	$AUC_{0\text{-tlast}}$ (ng.h/mL)	C_{max} (ng/mL)	T_{max} (h)
1	5	male	14776.3	6299.9	1.00
		female	8597.9	4237.6	1.00
	15	male	39752.7	13333.4	0.84
		female	43431.2	16870.1	1.00
	50	male	102302.0	45911.1	0.70
		female	79036.9	35203.0	1.00
42	5	male	11995.6	3831.0	1.00
		female	13579.7	4737.1	1.33
	15	male	26322.4	7847.7	0.83
		female	34587.6	14161.3	1.00
	50[a]	male	117585.2	102302.0	1.00
		female	63452.2	79036.9	0.95

Abbreviations: $AUC_{0\text{-tlast}}$ = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; C_{max} = maximum concentration; T_{max} = time to maximum concentration.
[a] The no observed adverse effect level

In 5 pharmacokinetic (PK) studies, effects of GB1211 on human ATP binding cassette transporters, single-dose absorption, tissue distribution, and elimination, protein binding, in vitro metabolism, and enzyme inhibition were evaluated. Results indicated that GB1211 is a

substrate of P-glycoprotein (P-gp), but not of breast cancer resistance protein (BCRP); and an inhibitor of BCRP, but not of P-gp. The mean free fractions of GB1211 in plasma were 14.1% (rabbit), 7.66% (mouse), 5.34% (human), 3.87% (dog), 1.22% (rat); and protein binding was not concentration dependent. Mean elimination half-lives from plasma were 1.46 (intravenous) and 3.04 hours (oral), with total plasma exposure ($AUC_{0\text{-}tlast}$) to [^{14}C]-GB1211-related radioactivity at 1170 (intravenous) and 13100 h.ng eq./g (oral). Oral bioavailability was 109%. In albino and pigmented mice, [^{14}C]-GB1211-related radioactivity was well absorbed and rapidly distributed into tissues, [^{14}C]-GB1211-related radioactivity was rapidly eliminated from tissues, and the mean overall recovery of the radioactivity administered was 103%. GB1211 showed a trend for distribution to the uveal tract and skin of pigmented mice. This was reversible and below the limit of quantification at 168 hours. (refer to Sections 4.2.3 and 4.2.5 of IB[6] for further information). The mean free fractions of GB1211 in human liver microsomes across GB1211 concentrations were similar at protein concentrations of 0.1 mg/mL (97.8%) and 1 mg/mL (67.6%), but at 5 mg/mL the free fraction was higher at 1 µM (61.5%) than at 10 µM (26.4%) and 100 µM (36.4%). The metabolic turnover (percent of parent remaining) of [^{14}C]-GB1211 was most extensive in dog, mouse, and rat hepatocytes; was lower in rabbit; and was negligible in human hepatocytes. No unique human in vitro metabolites were formed and the proportions of metabolites present in the human profiles were not greater than those observed in the other species. Enzyme activities mediated by cytochrome P450 (CYP)-1A2, CYP2C8, CYP2D6 and CYP3A4 were weakly inhibited by GB1211, and the inhibition was not considered to be metabolism dependent.

Further details from the nonclinical PK programme can be found in the IB.[6]

1.6. Summary of Clinical Experience

This study is a first-in-human study. No clinical studies have been performed with GB1211 to date.

1.7. Study Rationale

The principal aim of this study is to obtain safety and tolerability data when GB1211 is administered orally as single doses and as multiple doses to healthy subjects. In addition, an optional part has been included to obtain safety and tolerability data when GB1211 is administered orally as multiple doses to subjects with suspected NASH and liver fibrosis (refer to Section 3.1). This information, together with the PK data, will help establish the doses and dosing regimen suitable for future studies in subjects with the targeted indication. The effect of GB1211 on exploratory biomarkers will also be investigated, along with the effects of food on the PK of GB1211.

1.8. Benefit-risk Assessment

Healthy subjects and subjects with suspected NASH and liver fibrosis in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP), although there may also be some discomfort from collection of blood samples and other study procedures. More

information about the known and expected benefits, risks, and reasonably anticipated adverse effects associated with GB1211 may be found in the IB.[6]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objectives of the study are:

- to evaluate the safety and tolerability of single and multiple doses of GB1211 administered to healthy subjects.
- to evaluate the safety and tolerability of multiple doses of GB1211 administered to subjects with suspected NASH and liver fibrosis.

The secondary objectives of the study are:

- to evaluate the PK of single doses of GB1211 in plasma and urine in healthy subjects and the PK of multiple doses of GB1211 in plasma of healthy subjects and subjects with suspected NASH and liver fibrosis.
- to determine the effect of food on the single oral dose PK of GB1211.

The exploratory objectives of the study are:

- to investigate biomarkers related to GB1211 activity at single and/or multiple doses in comparison to placebo in healthy subjects and subjects with suspected NASH and liver fibrosis.
- to investigate biomarkers of metabolism, inflammation, and fibrosis following multiple doses of GB1211 in healthy subjects and/or subjects with suspected NASH and liver fibrosis.
- to identify metabolites of GB1211 in plasma and urine.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary safety endpoints for the study are as follows:

- incidence and severity of adverse events (AEs)
- incidence of laboratory abnormalities, based on haematology, clinical chemistry, and urinalysis test results
- 12-lead ECG parameters
- vital signs measurements
- physical examinations

2.2.2. Secondary Endpoints

For Part A, the single ascending dose (SAD) in healthy subjects, PK outcome endpoints of GB1211 are as follows:

- AUC from time zero to infinity ($AUC_{0-\infty}$)
- $AUC_{0\text{-tlast}}$
- C_{max}
- time of the maximum observed plasma concentration (T_{max})
- $t_{1/2}$
- apparent total plasma clearance (CL/F)
- apparent volume of distribution (V_z/F)
- amount of drug excreted in urine (A_e)
- percentage of dose excreted unchanged (f_e) in urine
- renal clearance (CL_R)

For Parts B and C, the multiple ascending doses (MAD) in healthy subjects and subjects with suspected NASH and liver fibrosis, PK outcome endpoints of GB1211 are as follows:

- AUC over a dosing interval ($AUC_{0-\tau}$)
- $AUC_{0-\infty}$
- C_{max}
- T_{max}
- $t_{1/2}$
- minimum observed plasma concentration (C_{min})
- observed accumulation ratio based on $AUC_{0-\tau}$ ($RA_{AUC0-\tau}$)
- observed accumulation ratio based on C_{max} (RA_{Cmax})

Other PK parameters may also be reported if necessary.

2.2.3. Exploratory Endpoints

- The following biomarkers related to the GB1211 activity and biomarkers of metabolism, inflammation, and fibrosis will be assessed as follows:
  - For all SAD and MAD cohorts (Parts A, B, and C):
    - Serum galectin-3
    - Chemokine (C-C motif) ligand (CCL)-4
    - Other biomarkers may also be measured in an exploratory fashion.

- For MAD cohorts only (Parts B and C):
  - Changes from baseline at Day 10 (healthy subjects) and Day 42 (subjects with suspected NASH and liver fibrosis) in fasting plasma glucose and insulin.
  - Changes from baseline at Day 10 (healthy subjects) and Day 42 (subjects with suspected NASH and liver fibrosis) in lipid profile.
  - Changes from baseline at Day 10 (healthy subjects) and Day 42 (subjects with suspected NASH and liver fibrosis) in heat shock C-reactive protein (hsCRP), interleukin (IL)-12, monocyte chemotactic protein (MCP)-1, and tumor necrosis factor (TNF)-α, as well as the proinflammatory chemokines, CCL2, CCL3, CCL4, and the chemokine receptors chemokine (C-C motif) receptor (CCR)-1 and CCR2; and other biomarkers of inflammation as required.
- For subjects with suspected NASH and liver fibrosis only (Part C, MAD cohort):
  - Changes from baseline at Day 42 in biomarkers of fibrosis, including but not limited to extracellular matrix proteins (tissue inhibitor of matrix metalloproteinase-1 [TIMP-1], hyaluronic acid [HA], and aminoterminal peptide of pro-collagen III [P3NP]), A9, E74-like transcription factor (ELF) panel, cytokeratin (CK)-18, plasminogen activator inhibitor (PAI)-1, chitinase-3 like protein-1 (CH3L1), IL6, and pro-collagen 3.
- Identification of GB1211 metabolites in plasma and urine.

3. INVESTIGATIONAL PLAN

This is a Phase 1, randomised, double-blind, placebo-controlled, first-in-human study in which the safety, tolerability, and PK of orally administered GB1211 will be assessed in healthy adult subjects and adult subjects with suspected NASH and liver fibrosis.

Suspected NASH is defined as the presence or history of fatty liver, together with elevated alanine aminotransferase (ALT; defined as ALT values ≥ 30 U/L in males or ≥ 20 U/L in females), plus either confirmed type 2 diabetes mellitus (T2DM) or metabolic syndrome (Adult Treatment Panel III definition), in the absence of any other liver disease. Additional criteria aim to enrich for individuals with liver fibrosis (as per inclusion criteria; Section 4.3).

The study will consist of 3 parts: a SAD phase (Part A) enrolling a total of 5 cohorts of healthy subjects; a MAD phase (Part B) enrolling 2 cohorts of healthy subjects; and an optional Part C MAD phase, enrolling 1 cohort of subjects with suspected NASH and liver fibrosis. One cohort of Part A will receive GB1211 under both fasted and fed conditions to investigate the effect of food.

3.1. Overall Study Design and Plan

3.1.1. Part A

Part A will comprise a single-dose, sequential-cohort study incorporating a single-cohort, randomised, 2-part arm to investigate the effect of food. Overall, 40 subjects will be studied in 5 cohorts (Cohort A1 to A5), with each cohort consisting of 8 subjects.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only, residing at the Clinical Research Unit (CRU) from Day -1 (the day before dosing) to Day 3 (48 hours postdose), except for the food-effect cohort (planned to be Cohort A3), where each subject will participate in 2 treatment periods separated by a minimum of 7 days.

All subjects will return for a Follow-up visit 5 to 7 days after their final dose.

Dose Regimen:

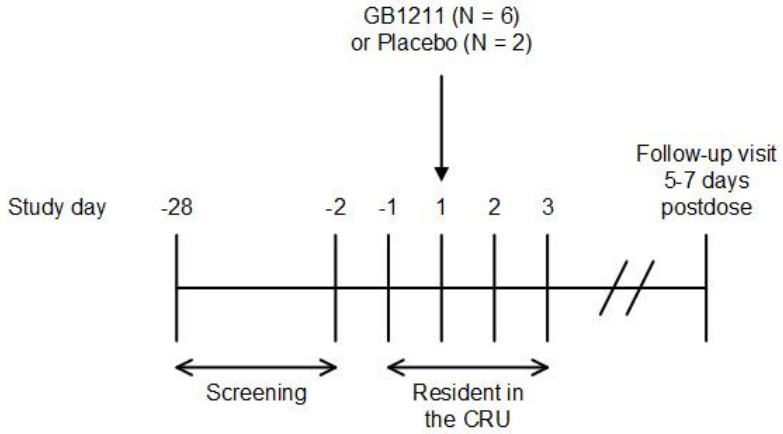
In each of Cohorts A1 to A5, 6 subjects will receive GB1211 and 2 will receive placebo. In all cohorts, except the food-effect cohort, all doses will be administered in the fasted state in accordance with a randomisation schedule on the morning of Day 1. For the food-effect cohort, which is planned to be Cohort A3, Treatment Period 1, Day 1 doses will be administered in the fasted state in accordance with the randomisation schedule and in Treatment Period 2, Day 1 doses will be given 30 minutes after the start of a high fat breakfast. Each subject in Cohorts A1 to A5 (except the food-effect cohort) will receive only a single dose of GB1211 or placebo during the study. In the food-effect cohort, subjects will receive the same treatment in both periods and will receive 2 single doses of GB1211 or placebo during the study.

In Cohorts A1 to A5 (except the fed period of the food-effect cohort), dosing will occur such that 2 subjects (1 active and 1 placebo) will be dosed at least 24 hours before the remaining subjects, where continuation to dose the remaining subjects will be at the Investigator's discretion.

Based on the ongoing review of the safety, tolerability, and PK results, additional nonresidential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond 28 days after each final dosing occasion.

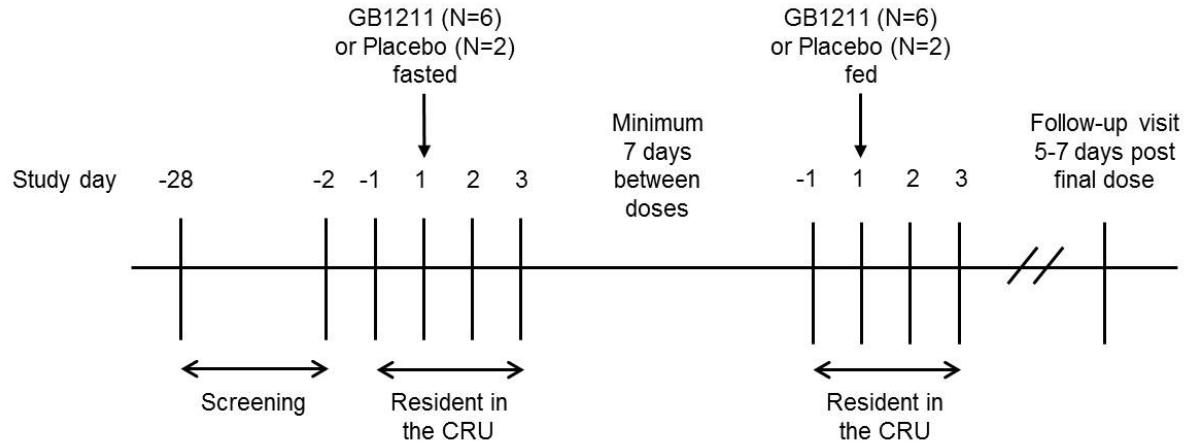
An overview of the study design is shown in Figure 1 and Figure 2 and the planned dose levels in Figure 3.

Figure 1: Study Schematic - Part A Cohorts (Except the Food-Effect Cohort)



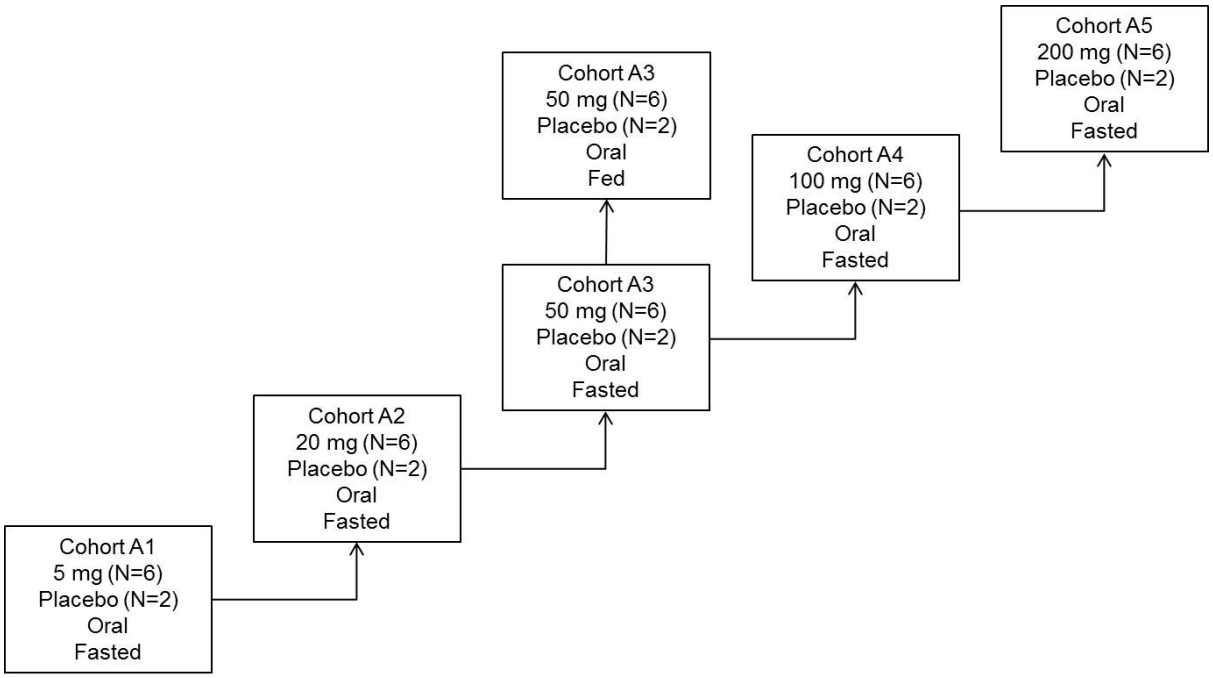
Abbreviation: CRU = Clinical Research Unit

Figure 2: Study Schematic - Part A Food-Effect Cohort (Planned to be Cohort A3)



Abbreviation: CRU = Clinical Research Unit

Figure 3: Planned Dose Levels (Part A)



The total duration of study participation for each subject (from Screening through Follow-up visit) for all Part A cohorts except the food-effect cohort is anticipated to be approximately 5 weeks. For each subject in the food-effect cohort (planned to be Cohort A3), the total duration is anticipated to be approximately 6 to 7 weeks.

3.1.2. Part B

Part B will comprise a multiple-dose, sequential-cohort study. Overall, 22 subjects will be studied in 2 cohorts (Cohorts B1 to B2), with each cohort consisting of 11 subjects. Dosing in

Part B will start following review of safety, tolerability, and PK data from a single dose with exposure higher than the predicted steady-state exposure.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 (the day before dosing) until the morning of Day 11 (24 hours after the final dose on Day 10).

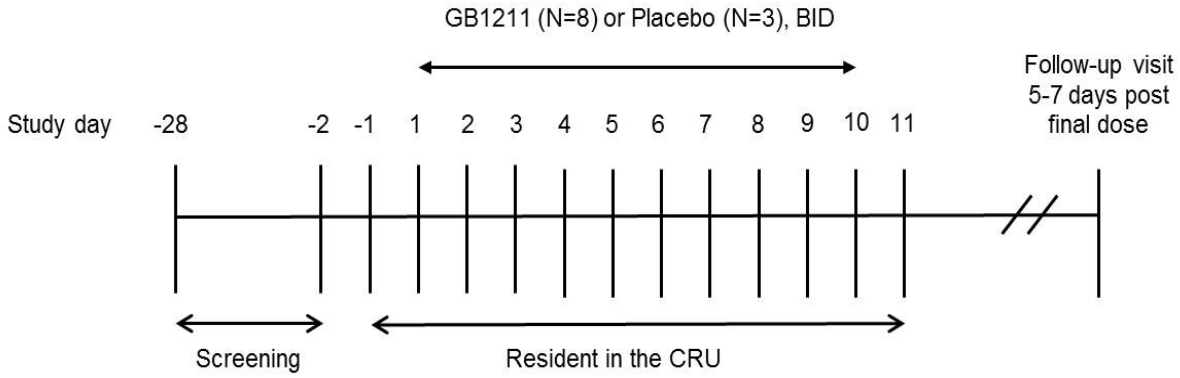
All subjects will return for a Follow-up visit 5 to 7 days after their final dose.

Dose Regimen:

In each of Cohorts B1 to B2, 8 subjects will receive GB1211 and 3 subjects will receive placebo. The dietary state for dosing in Part B will be fasted unless data from the food-effect cohort is available and supports dosing in the fed state. For all subjects, the planned dosing will be BID on Days 1 to 9, inclusive, and a final single dose administration will occur in the morning of Day 10. The dosing interval/frequency and dosing duration in Part B may be changed following review of data from cohorts in Part A (Section 3.4). The predicted total daily exposure will not exceed the highest exposure observed in Part A. There will be a minimum of 10 days between dose escalations for each cohort.

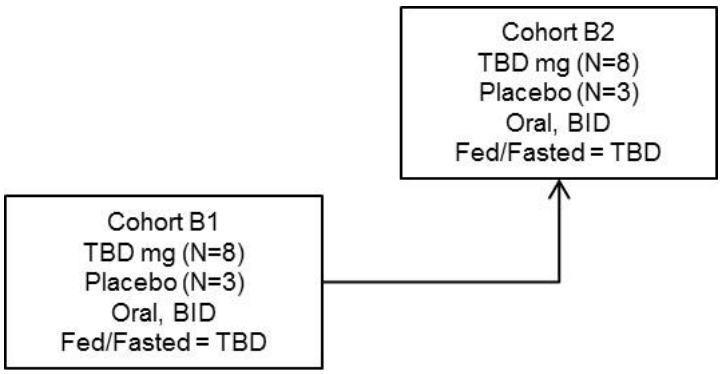
An overview of the study design is shown in Figure 4 and the planned dose levels in Figure 5.

Figure 4: Study Schematic (Part B)



Abbreviations: BID = twice-daily; CRU = Clinical Research Unit

Figure 5: Planned Dose Levels (Part B)



Abbreviations: BID = twice-daily; TBD = to be determined

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 6 to 7 weeks.

3.1.3. Part C (Optional)

Part C will comprise a multiple-dose cohort of 25 subjects with suspected NASH and liver fibrosis (Cohort C1). Part C may start following review of data from Part A and at least 1 Part B cohort.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 (the day before dosing) until the morning of Day 2, returning for nonresidential visits on Days 7, 14, 21, 28, and 35. Subjects will then check back into the CRU on Day 41 until the morning of Day 43 (24 hours after the final dose on Day 42).

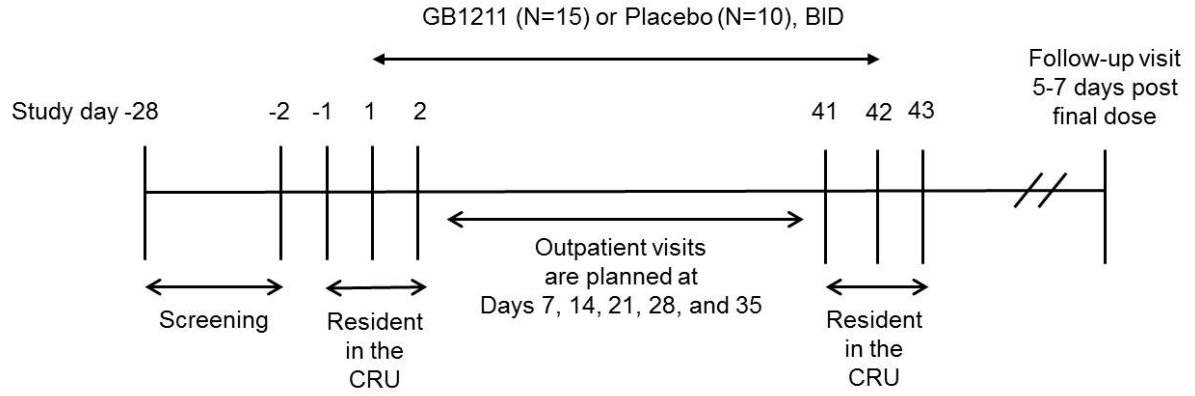
All subjects will return for a Follow-up visit 5 to 7 days after their final dose.

Dose Regimen:

For Part C, Cohort C1, 15 subjects will receive GB1211 and 10 subjects will receive placebo. The dietary state for dosing in Part C will be fasted unless data from the food-effect cohort is available and supports dosing in the fed state. For all subjects, the planned dosing will be BID on Days 1 to 41 inclusive, and a final single dose administration will occur in the morning of Day 42. The total daily dose administered, dose interval/frequency, and dosing duration will be based on review of data from Parts A and B.

An overview of the study design is shown in Figure 6.

Figure 6: Study Schematic (Part C)



Abbreviations: BID = twice-daily; CRU = Clinical Research Unit

The dose level of Part C is to be determined following completion of Part A and at least 1 cohort of Part B.

The total duration of study participation for each subject (from Screening through Follow-up visit) for Cohort C1 is anticipated to be approximately 11 weeks.

A Schedule of Assessments is presented in Appendix 6.

3.2. Study Start and End of Study Definitions

The start of the study is defined as the date the first subject, who is subsequently enrolled, signs an Informed Consent Form (ICF). The point of enrolment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Additional Groups

Following review of the safety, tolerability, and PK data, additional dose cohorts (where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7]) may be added to the study. Up to 3 further cohorts may be included in each of Parts A, B, and C. The requirement for additional cohorts will be agreed with the Sponsor and documented in the Trial Master File (TMF).

3.4. Discussion of Study Design, Including the Choice of Control Groups

For Parts A and B of the study, a sequential-cohort, ascending-dose design has been chosen for safety reasons as GB1211 is in the early stages of clinical development, with Part A of the study being the first time it will be administered to humans. Oral doses have been chosen for all parts of the study, as this is the intended clinical route of administration. A 2-part design has been chosen for the food-effect arm, as this gives a within-subject assessment of the influence of food on the PK of GB1211 and so increases the power of the study for the given number of subjects.

It is the intent of Part B to dose subjects such that steady-state plasma levels of GB1211 are achieved and maintained for several days. Based on the available nonclinical data, it is expected that this will be achieved following 9 days of BID dosing; however, a full review of all the safety, tolerability, and PK data from Part A will be performed to confirm the dose regimen for Part B. The dose regimen will comprise no less than once every day and will not exceed 4-times-daily dosing. The dosing duration will comprise no fewer than 7 consecutive days and will not exceed 14 consecutive days of dosing.

Conducting the initial single- and MAD in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

For Part C, it is the intent to dose subjects with suspected NASH and liver fibrosis to investigate safety, tolerability, PK, and the effect on specified exploratory biomarkers following multiple oral doses of GB1211 in subjects of the targeted indication. Preclinical toxicology data provides evidence for dosing over 42 days for Part C, and a study by Mudaliar et al., indicates that decreases in serum markers of fibrosis were observed following 6 weeks administration of obeticholic acid in NAFLD patients[7]; however, a full review of all the safety, tolerability, PK, and emerging exploratory biomarker data from Parts A and B will be performed to confirm the dose regimen for Part C.

Details of the dosing regimen and duration used for Parts B and C of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of each treatment period is considered adequate to achieve the study objectives. Where applicable, an interval of at least 7 days between treatment periods in the food-effect arm is considered adequate to prevent carryover of GB1211; however, may be adjusted based on emerging PK data.

This study will be double-blind and placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

Continuous 12-lead ECG monitoring will be included in this study in order to explore potential GB1211 effects on the QT interval, with a view of supporting a potential thorough QT study waiver.

3.4.1. Dose Interval

Following thorough review of all available nonclinical data (pharmacological and toxicological), dosing at each dose level in Part A will be such that 2 subjects (1 GB1211 and 1 placebo) will be dosed 24 hours before the remaining 6 subjects. After dosing the first 2 subjects on a separate day, a minimum of a 5-minute dosing interval for the remaining 6 subjects in each dose-ascending cohort is considered acceptable. Continuation to dose the remaining 6 subjects will be at the Investigator's discretion.

For Part B, sentinel dosing is not planned as the total daily dose administered will not exceed a dose shown to be safe and well tolerated in Part A. In addition, accumulation is not expected based on the available nonclinical data and therefore, predicted total daily exposure

in Part B will not exceed a well-tolerated exposure in Part A. However, following review of data in Part A, sentinel dosing may be introduced for Part B cohorts, if exposure is predicted to exceed the maximum exposure in Part A.

3.5. Selection of Doses in the Study

In the 42-day repeat oral dose toxicology studies, NOAELs in the mouse and the dog were 500 mg/kg/day and 50 mg/kg, respectively, corresponding to human equivalent doses (HEDs) of 40 and 27 mg/kg, respectively. Therefore applying a 10-fold safety margin the maximum recommended starting dose (MRSD) is 2.7 mg/kg, approximately 162 mg for a 60 kg subject. In vitro data in human cells suggests an IC_{50} of GB1211 of 0.1 µM (0.5 µg/mL) supporting the chosen MRSD.

In the PD study[6] evaluating the effect of GB1211 in carbon tetrachloride-induced liver fibrosis in mice there was no pharmacological activity observed at 2 mg/kg but there was activity at 10 mg/kg. Therefore the MRSD that is not considered to be pharmacologically active, based on the 2 mg/kg dose level, is 0.16 mg/kg, equivalent to approximately 9.6 mg in a 60 kg subject. The lowest pharmacologically active dose has been defined as 10 mg/kg, representing a HED of 48 mg for a 60 kg subject.

The proposed starting dose of 5 mg is 1.9-fold lower than the MRSD of 9.6 mg (based on the PD study[6]**)** and therefore is not expected to have any pharmacological activity.

The proposed IMP dose levels for the study are shown in Table 3. As described in Section 3.6 each dose following the starting dose may be subject to change based on review of data from previous cohorts.

Table 3: Proposed Investigational Medicinal Product Dose Levels

Study Part	Cohort	Subject Numbers	Treatment Period 1	Treatment Period 2
Part A	A1	101 – 108	5 mg or placebo (fasted)	
	A2	109 – 116	20 mg or placebo (fasted)	
	A3	117 – 124	50 mg or placebo (fasted)	50 mg or placebo (fed)
	A4	125 – 132	100 mg or placebo (fasted)	
	A5	133 – 140	200 mg or placebo (fasted)	
Part B	B1	201 – 211	TBD	
	B2	212 – 222	TBD	
Part C	C1	301 - 325	TBD	

Abbreviation: TBD = to be determined

For Part B of the study, dose levels, dosing frequency/interval, and dosing duration will be fully decided, in consultation with the Sponsor, on the basis of data from Part A of the study. For Part C of the study, dose levels, dosing frequency/interval, and dosing duration will be fully decided, in consultation with the Sponsor, on the basis of data from Part A, and at least 1 Part B cohort. The total daily dose of GB1211 administered during this part of the study will not exceed the maximum well-tolerated dose level studied in Part A.

Dose levels should not increase by more than 5-fold for predicted nonpharmacologically active dose levels and by 3-fold for predicted pharmacologically active dose levels.

The highest dose level may exceed the top dose shown in the above table, providing systemic exposure does not exceed that stated in the dose escalation stopping criteria (Section 3.7).

Details of all doses administered in Parts A, B, and C of the study will be documented in the TMF.

3.6. Dose Escalation

Doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety and tolerability data (up to 48 hours post-final dose) and PK data (up to 24 hours post-final dose) from the lower dose levels. Doses may be reduced and may be lower than the starting dose. There will be a minimum of 10 days between dose escalations to allow sufficient time for an adequate safety review.

Dose escalation in both Parts A and B will only occur if data from a minimum of 6 and 7 subjects, respectively, have been reviewed from the previous lower dose cohort, such that data from a minimum of 4 subjects who have received GB1211 will be used to make the dose escalation decision.

The justification for this is as follows:

- Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.
- A minimum of 4 subjects receiving the active drug is considered sufficient to characterise the safety profile and PK response to GB1211.

Between each dose escalation, the Investigator will review all available blinded data to ensure it is safe to proceed with the planned dose escalation. An interim safety report, summarising results from all available safety assessments, will be sent to the Sponsor prior to the start of each successive cohort. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PK data will also be reviewed in terms of dose escalation and to confirm that the study design remains appropriate. In the event of a disagreement between Sponsor and Investigator on the dose escalation decision, the decision of the Investigator will be upheld.

3.7. Dose Escalation Stopping Criteria

The study will be halted if 1 or more subjects experience an serious adverse event (SAE) that is considered to be related to IMP or 2 or more subjects experience severe AEs that are considered to be related to IMP. If, following an internal safety review, the Sponsor deems it appropriate to restart the study; this can be done following approval of a substantial protocol amendment.

In Parts A and B, following consultation with the Sponsor, dose escalation will stop if:

- One or more subjects in a cohort experience an SAE that is considered to be related to IMP or 2 or more subjects in a cohort experience severe AEs that are considered to be related to IMP.
- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a cohort that, in the opinion of the Investigator, warrant stopping of dose escalation.
- There is evidence of clinically significant increases in liver function tests (aspartate aminotransferase [AST], ALT, alkaline phosphatase, bilirubin, and/or gamma-glutamyl transferase), defined as 3 times the upper limit of normal (ULN) in 2 or more subjects in a cohort (confirmed with repeat testing), which are considered related to the IMP in the opinion of the Investigator.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a cohort.
- The systemic exposure for any individual subject is predicted to exceed a C_{max} of 19755 ng/mL and/or an AUC from time zero to 24 hours postdose (AUC_{0-24}) of 52486 ng.h/mL; ie, systemic exposure will be no greater than the lowest exposure at the NOAEL (Criterion is based on preclinical toxicology data from both male and female mice, where no gender differences were observed in terms of safety findings).

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria for Parts A: Healthy Subjects

Subjects for Part A must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Males or females, of any race, between 18 and 55 years of age, inclusive.
2. Body mass index (BMI) of 18.0 to 32.0 kg/m^2 (inclusive) with a minimum body weight of 50 kg.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhaemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening and Check-in as assessed by the Investigator (or designee), as applicable.
4. Resting heart rate ≥ 45 bpm and ≤ 90 bpm with a single 12-lead ECG at Screening.
5. Females will not be pregnant or lactating, and females of childbearing potential and males will agree to use contraception as detailed in Appendix 4.

6. Male subjects must agree to refrain from sperm donation and females should refrain from ova donation from the date of Check-in (Day -1) until 90 days after the Follow-up visit.
7. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Inclusion Criteria for Part B: Healthy Subjects

Subjects for Part B must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Males or females, of any race, between 18 and 60 years of age, inclusive.
2. Body mass index (BMI) of 18.0 to 32.0 kg/m^2 (inclusive) with a minimum body weight of 50 kg.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhaemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening and Check-in as assessed by the Investigator (or designee), as applicable.
4. Females will not be pregnant or lactating, and females of childbearing potential and males will agree to use contraception as detailed in Appendix 4.
5. Male subjects must agree to refrain from sperm donation and females should refrain from ova donation from the date of Check-in (Day -1) until 90 days after the Follow-up visit.
6. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.3. Inclusion Criteria for Part C: Subjects with Suspected NASH and Liver Fibrosis

Subjects for Parts C must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Males or females, of any race, between 18 and 60 years of age, inclusive.
2. Body mass index (BMI) of ≥ 25.0 and ≤ 38.0 kg/m^2.
3. Documented history of fatty liver within the last 24 weeks by one of the following: magnetic resonance imaging (MRI) suggesting liver fat ≥ 8%, ultrasound (US) indicating fatty liver, or Fibroscan Controlled Attenuation Parameter (CAP) > 270 dB/m. In subjects without a documented history of fatty liver, a Fibroscan CAP or US can be performed at Screening. Subjects with Fibroscan CAP > 270 dB/m or US indicating fatty liver are eligible.
4. Metabolic syndrome (Adult Treatment Panel III definition) or T2DM (defined as stable diabetes with glycosylated haemoglobin [HbA1c] ≤ 9.5%).
5. Alanine aminotransferase (ALT) ≥ 20 U/L for females and ≥ 30 U/L for males at Screening.
6. Fibroscan ≥ 7 KPa and < 13 KPa, or Fibrosis-4 (FIB-4) index ≥ 1.1 and < 3.25.

7. Females of nonchildbearing potential defined as permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) or postmenopausal (defined as at least 12 months postcessation of menses without an alternative medical cause and follicle-stimulating hormone [FSH] level ≥ 40 mIU/mL). Males will agree to use contraception as detailed in Appendix 4.
8. Male subjects must agree to refrain from sperm donation and females should refrain from ova donation from the date of Check-in (Day -1) until 90 days after the Follow-up visit.
9. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.4. Exclusion Criteria for Part A: Healthy Subjects

Subjects from Part A will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, haematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of febrile illness within 7 days prior to the first dose of study drug or subjects with evidence of active infection.
3. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
4. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair will be allowed, but not cholecystectomy).
5. Any of the following:
    a. QTcF > 450 msec confirmed by repeat measurement.
    b. QRS duration > 110 msec confirmed by repeat measurement.
    c. PR interval > 220 msec confirmed by repeat measurement.
    d. findings which would make QTc measurements difficult or QTc data uninterpretable.
    e. history of additional risk factors for torsades de pointes (eg, heart failure, hypokalaemia, family history of long QT syndrome).
6. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
7. Alcohol consumption of > 21 units per week for males and > 14 units per week for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
8. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.

9. Positive hepatitis panel and/or positive human immunodeficiency virus (HIV) test (Appendix 2).
10. Participation in a clinical study involving administration of an investigational agent or vaccine (new chemical entity) or having received a biological product in the past 90 days prior to dosing.
11. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to dosing, unless deemed acceptable by the Investigator (or designee).
12. Use or intend to use any prescription medications/products other than hormone replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives within 14 days prior to dosing, unless deemed acceptable by the Investigator (or designee).
13. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
14. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
15. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in, or positive cotinine at Screening or Check-in.
16. Receipt of blood products within 2 months prior to Check-in and donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
17. Poor peripheral venous access.
18. Have previously completed or withdrawn from this study investigating GB1211, and have previously received the investigational product.
19. Subject who, in the opinion of the Investigator (or designee), should not participate in this study.
20. Subject is not willing to minimise or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) following administration of study drug until 24 hours after the last dose.

4.5. Exclusion Criteria for Part B: Healthy Subjects

Subjects from Part B will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, haematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).

2. History of febrile illness within 7 days prior to the first dose of study drug or subjects with evidence of active infection.
3. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
4. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair will be allowed, but not cholecystectomy).
5. Clinically significant ECG abnormalities or QTcF greater than 450 msec for males and 470 msec for females at either Screening or Day 1 predose, or any prior history of QT abnormality.
6. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
7. Alcohol consumption of > 21 units per week for males and > 14 units per week for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
8. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.
9. Positive hepatitis panel and/or positive HIV test (Appendix 2).
10. Participation in a clinical study involving administration of an investigational agent or vaccine (new chemical entity) or having received a biological product in the past 90 days prior to dosing.
11. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to dosing, unless deemed acceptable by the Investigator (or designee).
12. Use or intend to use any prescription medications/products other than hormone replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives within 14 days prior to dosing, unless deemed acceptable by the Investigator (or designee).
13. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
14. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
15. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in, or positive cotinine at Screening or Check-in.
16. Receipt of blood products within 2 months prior to Check-in and donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
17. Poor peripheral venous access.

18. Have previously completed or withdrawn from this study investigating GB1211 and have previously received the investigational product
19. Subject who, in the opinion of the Investigator (or designee), should not participate in this study.
20. Subject is not willing to minimise or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) following administration of study drug until 24 hours after the last dose.

4.6. Exclusion Criteria for Part C: Subjects with Suspected NASH and Liver Fibrosis

Subjects from Part C will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. If diabetic and diabetes is other than T2DM.
2. Subjects, who have had bariatric surgery of any kind or, in the opinion of the Investigator, have experienced a clinically significant change in body weight within the 3 months prior to Screening.
3. History of any known serious disease (such as cancer, except skin basocellular carcinomas, major infection, clinically significant gastrointestinal disorder, major autoimmune disease) or other disease which in the Investigator's opinion would exclude the patient from the study.
4. The following clinical laboratory results at Screening:
   - Total Bilirubin > 2 × ULN
   - ALT > 155 U/L for females and > 185 U/L for males
   - AST > 155 U/L for females and > 200 U/L for males
5. Other abnormal clinical laboratory values that are considered clinically significant for this population.
6. History of febrile illness within 7 days prior to the first dose of study drug or subjects with evidence of active infection.
7. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
8. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy, cholecystectomy, and hernia repair will be allowed).
9. Clinically significant ECG abnormalities or QTcF greater than 450 msec for males and 470 msec for females at either Screening or Day 1 predose, or any prior history of QT abnormality.
10. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
11. Alcohol consumption of > 14 units per week for males and for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.

12. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.
13. Positive hepatitis panel and/or positive HIV test (Appendix 2).
14. Clinically significant laboratory abnormalities, as determined by the Investigator.
15. A creatinine clearance of less than 50 mL/min (as calculated by Cockcroft-Gault equation) or estimated glomerular filtration rate (eGFR) < 60 mL/[min*1.73 m²] at Screening.
16. Participation in a clinical study involving administration of an investigational agent or vaccine (new chemical entity) or having received a biological product in the past 90 days prior to dosing.
17. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to dosing, unless deemed acceptable by the Investigator (or designee).
18. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
19. Subject taking any antidiabetic medications, with the exception of metformin, sulfonylureas, gliptins, and sodium/glucose co-transporter 2 inhibitors, within 3 months prior to Screening.
20. Use of any of the following non-permitted medication within 6 months prior to Screening: amiodarone, bile salt chelators, methotrexate, pharmacological doses of systemic corticosteroids for at least 2 consecutive weeks, or any other medications known to affect liver function.
21. Use or intend to use any nonprescription medications/products including vitamins (Vitamin E at dose <400 U is permitted, Vitamin E at dose 400 U is allowed if on a stable dose for 2 months prior), minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
22. Receipt of blood products within 2 months prior to Check-in and donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
23. Poor peripheral venous access.
24. Have previously completed or withdrawn from this study investigating GB1211, and have previously received the investigational product.
25. Subject who, in the opinion of the Investigator (or designee), should not participate in this study.
26. Subject is not willing to minimise or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) following administration of study drug until 24 hours after the last dose.

For Parts A and B, subjects may previously have been screened on a generic basis to determine their eligibility for inclusion in Phase I clinical studies conducted at the CRU. If generic screening was performed within the specified study screening window, selected study-specific procedures will be repeated either at an additional Screening visit or on admission to the CRU on Day -1.

4.7. Subject Number and Identification

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number at the time of first dose/dosing. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, in Part A Subjects 0101, 0102, etc, in Part B Subjects 0201, 0202, etc, in Part C Subjects 0301, 0302, etc). Replacement subjects (Section 4.8) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.8. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee).
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee).
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

In the event of confirmed results for any of the following criteria, dosing of a subject with the IMP will be stopped permanently:

- QTcF increases > 60 msec compared to baseline (predose) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement).
- Systemic exposure for any individual subject is predicted to exceed a C_{max} of 19755 ng/mL and/or an AUC_{0-24} of 52486 ng.h/mL; ie, systemic exposure will be no greater than the lowest exposure at the NOAEL.
- Liver chemistry results:
    1. ALT or AST > 5 x ULN, which is confirmed by repeat
    2. ALT or AST > 3 x ULN, which is confirmed and total bilirubin > 2 x ULN or international normalised ratio >1.5
    3. ALT or AST > 3 x ULN, which is confirmed and the new appearance (ie, onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash,

or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation/injury.

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilised.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will generally not be replaced.

4.9. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- adverse events unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration).
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms).
- medical or ethical reasons affecting the continued performance of the study.
- difficulties in the recruitment of subjects.
- cancellation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labelling

The IMPs (5 and 50 mg GB1211 and placebo capsules) will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificates of Analysis. A Certificate of Release authorised by a Qualified Person in the EU will also be issued for the IMP.

The IMP will be provided in high-density polyethylene bottles and stored according to the instructions on the label. The IMPs will be stored at the study site in a location that is locked with restricted access.

The bulk drug container and unit dose containers will be labelled in accordance with national laws and regulations. The IMPs will be transferred from bulk supplies into the subject's dose container by qualified clinical staff.

Capsules for the planned dose levels in Part A of the study will be assembled as shown in Table 4.

Table 4: Capsule Assembly for Part A

Cohort	Dose Level (mg)	Number of Capsules to be Assembled	
		Dose of GB1211	Placebo
A1	5	1 x 5 mg	1 x capsules
A2	20	4 x 5 mg	4 x capsules
A3	50	1 x 50 mg	1 x capsules
A4	100	2 x 50 mg	2 x capsules
A5	200	4 x 50 mg	4 x capsules

5.2. Study Treatment Administration

Each dose of GB1211 and placebo will be administered orally with approximately 240 mL of room temperature water. In Part A, all doses will be administered after an overnight fast of at least 10 hours, with the exception of the food-effect cohort (planned to be Cohort A3), where the dose given in Treatment Period 2 will be administered 30 minutes after starting a high-fat breakfast. The dietary status for dosing in Parts B and C will be fasted unless data from the food-effect cohort is available and supports dosing in the fed state.

Subjects in Part A and B will be administered the IMP in numerical order while standing and will not be permitted to lie supine for 2 hours after dosing, except as necessitated by the occurrence of an AE(s) and/or study procedures.

In Part C, the doses of GB1211 (taken at the site) on Days 1/2 and Days 41/42 will be administered to subjects at the study site while standing and will not be permitted to lie supine for 2 hours after dosing, except as necessitated by occurrence of an AE(s) and/or study procedures; but all other doses will be administered by the subject at home.

5.3. Randomisation

For Parts A and B, the randomisation code will be produced by the statistics department at Covance using a computer-generated pseudo-random permutation procedure. Randomisation for Part C is to be confirmed.

In Part A, 2 subjects per cohort will be randomly assigned to receive placebo. For all cohorts in Part A (except the fed treatment period of the food-effect cohort), sentinel dosing will occur whereby 2 subjects (1 active and 1 placebo) will be dosed on 1 day and, providing no safety concerns arise, the remaining 6 subjects will be dosed after 24 hours.

Subjects in the food-effect cohort (planned to be Cohort A3) will be randomised to receive the same treatment in Treatment Periods 1 and 2.

In Part B, 3 subjects per cohort will be randomly assigned to receive placebo, and in Part C, 10 subjects in Cohort C1 will be randomly assigned to receive placebo.

Prior to the start of the study, live randomisation code will be distributed according to the randomisation specification form and will include the Covance CRU pharmacy staff.

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo capsules will be identical in appearance to the GB1211.
- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomisation code during the assembly procedure.
- Interim bioanalytical data will be provided to Covance in a blinded manner.
- Where possible, exploratory biomarker data will be provided to Covance in a blinded manner.

To maintain the blind, the Investigator will be provided with a sealed randomisation code for each subject, containing details of their treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. In order to manage subject safety or to support dose escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code-break with the Sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance for Parts A and B:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed on the dose containers.

For Part C, treatment compliance will be assessed based on the number of capsules provided on Day 1 compared to the number of capsules returned on Day 42.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

6.1.1. Concomitant Therapies for Parts A and B

Subjects of Part A and B will refrain from use of any prescription or nonprescription medications/products during the study until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days), hormone replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications.

The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.1.2. Concomitant Therapies for Part C

Subjects of Part C will refrain from use of any prescription or nonprescription medications/products during the study with exceptions, as stated in Section 4.6, until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) and hormone replacement therapy are acceptable concomitant medications.

The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

6.2.1. Parts A and B

While confined at the study site for Parts A and B, subjects will receive a standardised diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations.

On the days with intensive PK assessments (Day 1 for Part A and Days 1 and 10 for Part B), meals will be identical for each cohort, with the exception of the high-fat breakfast for the food-effect cohort (planned to be Cohort A3).

On Day 1 in Part A, subjects will be fasted for at least 10 hours prior to study drug administration until 4 hours postdose, when a meal will be provided (lunch times on Day 1 will be staggered between subjects to ensure this). With the exception of water given with the dose, subjects will not be allowed fluids from 1 hour prior to until 2 hours after dosing. Meals will be provided as appropriate at other times. Other than the fluid restrictions on dosing days, water will be freely available at all times.

For the food-effect cohort (planned to be Cohort A3), subjects receiving the GB1211 or placebo under fed conditions will consume the following high-fat breakfast (Table 5) before dosing. Subjects should start the meal 30 minutes prior to administration of the IMP. Study subjects should eat this meal in 30 minutes or less. The drug product should be administered 30 minutes after start of the meal.

Table 5: High-fat Breakfast Content

High-fat Breakfast
120 g fried eggs (2 eggs) in vegetable oil
50 g bacon (2 rashers)
72 g toasted white bread (2 slices)
13 g butter (2 pats)
108 g hash brown (3 each)
240 g whole milk
Total calories: 973 kcal

This high-fat meal contains the equivalent of approximately 150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories.

In Part B, the time interval between meals and dosing will be determined by the PK data from Part A and will be documented in the TMF. Meals will be provided as appropriate at other times. With the exception of water given with the dose, subjects will not be allowed fluids from 1 hour prior to dosing until 2 hours after dosing. Other than these fluid restrictions, water will be freely available at all times.

For Parts A and B, foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in until the Follow-up visit. Caffeine-containing foods and beverages will not be allowed from 36 hours before Check-in until Discharge.

Consumption of alcohol will not be permitted from 36 hours prior to Check-in until the Follow-up visit.

6.2.2. Part C

While confined at the study site for Part C (Days -1 to 2 and Days 41 to 43), subjects will receive a standardised diet at scheduled times that do not conflict with other study-related

activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests.

On the days with intensive PK assessments (Days 1 and 42), every effort will be made to ensure within a subject that they have the same meal on these PK assessment days.

The time interval between meals and dosing will be determined by the PK data from Part A and will be documented in the TMF. During the residential or nonresidential visits, meals will be provided as appropriate at other times. With the exception of water given with the dose, subjects will not be allowed fluids from 1 hour prior to dosing until 2 hours after dosing. Other than these fluid restrictions, water will be freely available at all times.

From 7 days prior to Check-in until the Follow-up visit, foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed. Caffeine-containing foods and beverages will not be allowed from 36 hours before each site visit.

Consumption of alcohol will not be permitted from 36 hours prior to each site visit. During the rest of study, the patient should limit alcohol consumption to 2 units per day.

6.3. Smoking

For Parts A and B, subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Check-in until the Follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before Check-in until the Follow-up visit and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the Follow-up visit.

6.6. Exposure to Ultraviolet Light

Subjects should minimise or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) following administration of study drug until 24 hours after the last dose. If subjects need to be outdoors during this period, they should wear loose fitting clothes that protect skin from sun exposure and discuss other sun protection measures with the Investigator.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- blood samples
- urine samples (Part A only) (for GB1211 assay)
- any other procedures (ECGs will be scheduled before vital signs measurements).

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, blood draws.

7.1. Pharmacokinetic Assessments

7.1.1. Sample Collection and Processing

Blood samples (approximately 1 × 4 mL) will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. Furthermore, up to 3 additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analysed.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

Urine samples for Part A will be collected into preweighed polyethylene containers over the time intervals indicated in the Schedule of Assessments in Appendix 6. Procedures for collection, processing, and shipping of PK urine samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Plasma and urine concentrations of GB1211 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

An exploratory analysis of GB1211 metabolites in plasma and urine may be performed utilising the blood and urine samples collected for PK evaluation. If performed, the results of this analysis will be reported separately to the clinical study report.

7.2. Exploratory Biomarker Assessments

Biomarkers (as listed in Section 2.2.3) in which to assess the exploratory objectives include:

- Serum galectin-3
- CCL4
- Fasting plasma glucose and insulin
- Lipid profile (eg, low density lipoprotein [LDL], high density lipoprotein [HDL], total cholesterol, triglycerides)
- hsCRP, IL-12, MCP1, and TNF-α, as well as the proinflammatory chemokines, CCL2, CCL3, CCL4, and the chemokine receptors CCR1 and CCR2; and other biomarkers of inflammation as required
- Exploratory biomarkers related to fibrosis will include but are not limited to extracellular matrix proteins (TIMP-1, HA, and P3NP), A9, ELF panel, CK18, PAI-1, CH3L1, IL6, and pro-collagen 3

The list of biomarkers for the exploratory endpoints may be subject to change based on ongoing review of the data.

The timings of all exploratory biomarker assessments to be performed (as described in Section 2.2.3) during the study are indicated in the Schedule of Assessments in Appendix 6 and may be subject to change based on the ongoing review of the data.

Blood samples for these assessments will be collected by venipuncture or cannulation, with blood volumes including 3 additional blood samples if required (each subject per treatment period) detailed in Appendix 3. To avoid potential issues with repeat freeze thawing, samples of serum will be aliquoted into a minimum of 2 but ideally 3 aliquots. Samples for biomarker analysis will be shipped to an alternate site (to be determined) for analysis, and may be kept for future analysis of other exploratory biomarkers.

Any changes to the scheduled times of biomarker assessments will be agreed with the Sponsor and documented in the TMF.

7.3. Safety and Tolerability Assessments

Additional safety and tolerability assessments as described below will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

7.3.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final Discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you

were last asked?", at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject's source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator's (or designee's) opinion of the relationship to study drug.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilised. This will be completed at the Investigator's (or designee's) discretion.

7.3.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, haematology, urinalysis, serology [including coagulation parameters for Part C]) at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Subjects will be asked to provide urine samples for drugs of abuse screen and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.3.3. Vital Signs

Supine blood pressure, supine pulse rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 predose blood pressure and pulse rate will be measured in triplicate at approximately 2-minute intervals. The median value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges. Oral body temperature will be measured singly.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

7.3.4. Electrocardiogram

7.3.4.1. 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF value > 500 msec
- QTcF change from the baseline (predose) is > 60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

Day 1 predose 12-lead ECGs will be measured in triplicate at approximately 2-minute intervals. The mean value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

7.3.4.2. Telemetry

Cardiac rhythm will be monitored by telemetry at the times indicated in the Schedule of Assessments in Appendix 6.

Telemetry is not planned for Parts B and C of the study but may be implemented if any clinically significant findings are identified in the data from Part A.

7.3.4.3. Continuous 12-lead Electrocardiogram Monitoring for Part A

Continuous 12-lead ECG monitoring using a digital recorder will take place at the times indicated in the Schedule of Assessments in Appendix 6. Continuous 12-lead ECG monitoring will not be performed in the fed treatment period in Part A.

All continuous ECG data collected on study will be archived without extraction or analysis and will not be reported in the scope of this study.

Subjects will be supine for at least 10 minutes before the extraction timepoint and for 5 minutes from the start of each extraction timepoint (each extraction will last for 5 minutes). Environmental distractions (eg, television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

When coinciding, vital signs assessments and PK sampling should always be performed after the ECG extraction time window. If a separate ECG machine is being used for safety assessments described in Section 7.3.4.1, that machine should be in place prior to the extraction window to permit safety ECGs to be recorded irrespective of the extraction window. If the machine is not in place prior to the extraction window, safety ECGs must be

recorded after the extraction window. If an integral system is used, safety ECGs may be recorded irrespective of the extraction window.

7.3.5. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6. Full physical examination will usually only be performed at Screening.

7.3.6. Body Weight

Body weight (in underclothes) will be recorded at the times indicated in the Schedule of Assessments in Appendix 6.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time GB1211 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study.

8.2. Analysis Populations

8.2.1. Safety Population

The safety population will include all subjects who received at least 1 dose of study treatment (GB1211 or placebo).

8.2.2. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of GB1211 and have evaluable PK data. A subject will be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2-times median time to maximum concentration.

8.2.3. Biomarker Population

The biomarker population will include all subjects who received at least 1 dose of study treatment (GB1211 or placebo) and have at least 1 postdose biomarker assessment.

8.3. Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma and urine (Part A only for urine) concentration data, using commercial software such as Phoenix® WinNonlin®.

Plasma and urine concentrations (Part A only for urine) of GB1211 and PK parameters will be listed and summarised using descriptive statistics. Individual and mean GB1211 concentration-time profiles will also be presented graphically.

In Part A, where data are available, GB1211 dose proportionality will be examined across dose cohorts. The PK parameters will be analysed for dose proportionality using a power model approach or analysis of variance (ANOVA) model as appropriate. Where data are available, the effect of food at 1 dose level in Part A will be investigated using ANOVA.

In Part B, the PK parameters on Day 10 will be analysed for dose proportionality using a power model approach or ANOVA model as appropriate.

8.4. Exploratory Biomarker Analyses

Exploratory biomarker data will be listed and summarised using descriptive statistics. No formal statistical analysis of exploratory biomarker data is planned.

8.5. Safety Analysis

Safety parameters will be listed and summarised using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

8.6. Interim Analysis

No formal interim analyses are planned for this study.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- **Severe**: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesised cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the investigational medicinal

product (IMP) or study procedures at the Follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilised. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalisation

Adverse events requiring hospitalisation should be considered serious. In general, hospitalisation signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the Clinical Research Unit (CRU). When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered as serious.

Hospitalisation for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Covance Drug Safety Solutions (DSS) are responsible for coordinating the reporting of SAEs in accordance with the European Directive 2001/20/EC.

The Investigator will complete an SAE report form and forward it by facsimile or email to DSS and the Sponsor immediately (within 24 hours) upon becoming aware of an SAE.

The responsibilities of Covance DSS include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable CRU standard operating procedure on SAE reporting, the Safety Management Plan will always take precedence.
- Receive and review SAE report forms from the CRU and inform the Sponsor of the SAE within 2 working days of the initial notification to DSS. Drug Safety Services will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Covance's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all Suspected Unexpected Serious Adverse Reactions and forward to the Ethics Committee, Medicines and Healthcare Products Regulatory Agency, Principal Investigator, and the Sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the Sponsor 28 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfil regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and foetus.

Appendix 2: Clinical Laboratory Evaluations

<table>
<tr><th>Clinical chemistry:</th><th>Haematology:</th><th>Urinalysis:</th></tr>
<tr><td>Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Calcium
Chloride
Total Cholesterol
High density lipoprotein Cholesterol
Low density lipoprotein Cholesterol
Creatinine[a]
Direct bilirubin
Gamma-glutamyl transferase
Glucose
Inorganic phosphate
Potassium
Sodium
Total bilirubin
Total protein
Triglycerides
Urea</td><td>Haematocrit
Haemoglobin
Mean cell haemoglobin
Mean cell haemoglobin concentration
Mean cell volume
Platelet count
Red blood cell (RBC) count
White blood cell (WBC) count
WBC differential:
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils

Coagulation profile[f]:

Activated partial thromboplastin time
International normalised ratio
Prothrombin time</td><td>Blood
Glucose
Ketones
pH
Protein
Specific gravity
Urobilinogen
Microscopic examination</td></tr>
<tr><th>Serology[b]:</th><th>Drug screen[c]:</th><th>Hormone panel - females only:</th></tr>
<tr><td>Hepatitis B surface antigen
Hepatitis C antibody
Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen</td><td rowspan="3">Including but not limited to:
Amphetamines/methamphetamines
Barbiturates
Benzodiazepines
Cocaine (metabolite)
Methadone
Phencyclidine
Opiates
Tetrahydrocannabinol/ cannabinoids
Tricyclic antidepressants
Cotinine test[g]

Alcohol breath test[c]</td><td rowspan="3">Follicle-stimulating hormone[d]
Serum pregnancy test (human chorionic gonadotropin)[d]
Urine pregnancy test[e]</td></tr>
<tr><th>Other:</th></tr>
<tr><td>Glycosylated haemoglobin (HbA1c)[f]</td></tr>
</table>

[a] Creatinine clearance only to be analysed for Part C and at Screening.
[b] Only analysed at Screening.
[c] Only analysed at Screening and Check-in.
[d] Performed at Screening for all females.
[e] Performed for all females at Check-in and post-dosing. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[f] Part C only.
[g] Parts A and B only.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject in Part A (except the food-effect cohort [planned to be Cohort A3]).

	Volume per blood sample (mL)	Planned number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations	7.5	4	30
Serology	3.5	1	3.5
GB1211 pharmacokinetics	4	14	56
Exploratory biomarker assessments (eg, serum galectin-3 and chemokine C-C motif ligand-4 [CCL4])	4	2	8
	Total:		97.5

If extra blood samples are required (as per Sections 7.1, 7.2, and 7.3), the maximum blood volume to be withdrawn per subject will not exceed the volume of a standard blood donation.

The following blood volumes will be withdrawn for each subject in the food-effect cohort of Part A (planned to be Cohort A3).

	Volume per blood sample (mL)	Planned number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations	7.5	6	45
Serology	3.5	1	3.5
GB1211 pharmacokinetics	4	28	112
Exploratory biomarker assessments (eg, serum galectin-3 and CCL4)	4	4	16
	Total:		176.5

If extra blood samples are required (as per Sections 7.1, 7.2, and 7.3), the maximum blood volume to be withdrawn per subject will not exceed the volume of a standard blood donation.

The following blood volumes will be withdrawn for each subject in Part B.

	Volume per blood sample (mL)	Planned number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (including exploratory biomarker assessment of lipid profile and glucose)	7.5	8	60
Serology	3.5	1	3.5
GB1211 pharmacokinetics	4	27	108
Exploratory biomarker assessment - serum galectin-3	4	2	8
Exploratory biomarker assessment - insulin	4	2	8
Exploratory biomarker assessments - inflammation (eg, proinflammatory chemokines [including CCL4] and heat shock C-reactive protein [hsCRP], interleukin-12 [IL-12], and tumor necrosis factor [TNF]-α; and other biomarkers of inflammation as required)	10	2	20
	Total:		207.5

If extra blood samples are required (as per Sections 7.1, 7.2, and 7.3), the maximum blood volume to be withdrawn per subject will not exceed the volume of a standard blood donation.

The following blood volumes will be withdrawn for each subject in Part C.

	Volume per blood sample (mL)	Planned number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (including exploratory biomarker assessment of lipid profile and glucose)	7.5	8	60
Serology	3.5	1	3.5
Coagulation	1.8	6	10.8
GB1211 pharmacokinetics	4	22	88
Exploratory biomarker assessment - serum galectin-3	4	4	16
Exploratory biomarker assessment - insulin	4	4	16
Exploratory biomarker assessments - inflammation (eg, proinflammatory chemokines [including CCL4] and hsCRP, IL-12 and TNF-α; other biomarkers of inflammation as required) and exploratory biomarkers of fibrosis	10	2	20
	Total:		214.3

If extra blood samples are required (as per Sections 7.1, 7.2, and 7.3), the maximum blood volume to be withdrawn per subject will not exceed the volume of a standard blood donation.

Appendix 4: Contraception Guidance

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilisation to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-oestrogens, or selective oestrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception.

Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the Informed Consent Form until 90 days after the Follow-up visit. Primary (non-barrier) methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
  - bilateral tubal ligation
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes

- hormonal implant
- hormonal or non-hormonal intrauterine device
- vasectomised male partner (sterilisation performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject)

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects of childbearing potential should refrain from donation of ova from Check-in (Day -1) until 90 days after the Follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Check-in until 90 days after the Follow-up visit. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide

An acceptable second method of contraception for male subjects is vasectomy that has been performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success.

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the Follow-up visit. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the Follow-up visit.

Sexual Abstinence and Same-sex Relationships

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 90 days after the Follow-up visit.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the Follow-up visit.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.
- Notifying the EC of serious adverse events or other significant safety findings as required by EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigators will be redacted according to applicable laws and regulations.

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 also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organisation (CRO) auditors or other authorised personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk

management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.

- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorised 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 in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. 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.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognised (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions including, without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential

information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 6: Schedule of Assessments

Table 1: Schedule of Assessments – Part A (Single Dose)

Study Procedures	Screening	Treatment Period 1 (and 2 for Food-Effect Cohort)		Follow-up (5-7 days Postdose)
		Day -1	Days 1 to 3	
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Demographic data	X			
Medical history	X	X[a]		
Urinary drug screen	X	X		
Alcohol breath test	X	X		
Serology	X			
Pregnancy test[b]	X	X		X
Follicle-stimulating hormone	X[e]			
Height and body weight	X			
Study residency:				
Check-in		X		
Check-out			Day 3 (48 hours postdose)	
Nonresidential visit	X			X
Study drug administration:				
GB1211 or placebo			Day 1 (0 hours) (30 minutes after starting a high-fat breakfast in Treatment Period 2 for food-effect cohort [planned to be Cohort A3])	
Pharmacokinetics:				
Blood sampling			Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose	
Urine sampling			Predose (spot collection) and 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours postdose	
Exploratory biomarker assessments:				

Table 1: Schedule of Assessments – Part A (Single Dose)

Study Procedures	Screening	Treatment Period 1 (and 2 for Food-Effect Cohort)		Follow-up (5-7 days Postdose)
		Day -1	Days 1 to 3	
Blood sample for biomarker assessments (eg, serum galectin-3 and CCL4)			Predose and 24 hours postdose	
Safety and tolerability:				
Adverse event recording	X	X	Ongoing	X
Prior/concomitant medication monitoring	X	X	Ongoing	X
Clinical laboratory evaluations	X	X	48 hours postdose	X
Vital sign measurements (blood pressure, pulse rate, and oral body temperature)	X		Predose, 1, 2, 4, 8, 24, and 48 hours postdose	X
12-lead ECG	X		Predose, 1, 4, 24, and 48 hours postdose	X
Telemetry			From at least -1 hour predose to 4 hours postdose	
Continuous 12-lead ECG			X[c]	
Physical examination	X	X[d]	Prior to discharge[d]	X[d]

Abbreviations: CCL4 = chemokine (C-C) motif ligand 4; ECG = electrocardiogram.
[a] Interim medical history.
[b] In all females. Performed in serum at Screening and in urine at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[c] Monitor for 12-lead ECG recording will be worn from 2 hours predose to 25 hours postdose on Day 1. Extraction timepoints will be 60, 45, and 30 minutes predose (averaged for baseline) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 postdose. Continuous 12-lead ECG recording will only be performed in the fasted treatment periods.
[d] Symptom-directed physical examination.
[e] In all females.

Table 2: Schedule of Assessments – Part B (Multiple Dose)

Study Procedures	Screening	Day -1	Days 1 to 11	Follow-up (5-7 days Post-Final Dose)
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Demographic data	X			
Medical history	X	X[a]		
Urinary drug screen	X	X		
Alcohol breath test	X	X		
Serology	X			
Pregnancy test[c]	X	X		X
Follicle-stimulating hormone	X[f]			
Height and body weight	X	X[e]		X[e]
Study residency:				
Check-in		X		
Check-out			Day 11 (24 hours postdose)	
Nonresidential visit	X			X
Study drug administration:				
GB1211 or placebo			Day 1 to 9 (0 and 12 hour) and Day 10 (0 hour)[b]	
Pharmacokinetics:				
Blood sampling			Day 1: pre-am dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-am dose Days 4 to 9: pre-am dose Day 10: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours post-final dose Day 11: 24 hours post-final dose	
Exploratory biomarker assessments:				

Table 2: Schedule of Assessments – Part B (Multiple Dose)

Study Procedures	Screening	Day -1	Days 1 to 11	Follow-up (5-7 days Post-Final Dose)
Serum galectin-3			Day 1: pre-am dose Day 10: predose	
Fasting glucose and insulin			Day 1: pre-am dose Day 10: predose	
Lipid profile (eg, LDL, HDL, total cholesterol, and triglycerides)			Day 1: pre-am dose Day 10: predose	
hsCRP, IL-12, TNF-α, MCP-1 and proinflammatory chemokines (CCL2, CCL3, CCL4, and the chemokine receptors CCR1 and CCR2); and other biomarkers of inflammation as required			Day 1: pre-am dose Day 10: predose	
Safety and tolerability:				
Adverse event recording	X	X	Ongoing	X
Prior/concomitant medication monitoring	X	X	Ongoing	X
Clinical laboratory evaluations	X	X	Days 4 and 6: pre-am dose Day 11: 24 hours post-final dose	X
Vital sign measurements (blood pressure, pulse rate, and oral body temperature)	X		Day 1: pre-am dose, 2, 4, and 8 hours post-am dose Days 2 to 9: pre-am dose Day 10: predose, 2, 4, and 8 hours post-final dose	X
12-lead ECG	X		Day 1: pre-am dose and 4 hours post-am dose Day 5: pre-am dose and 4 hours post-am dose Day 10: predose and 4 hours post-final dose	X
Physical examination	X	X[d]	Prior to Discharge on Day 11[d]	X[d]

Abbreviations: CCL = chemokine (C-C motif) ligand; CCR = chemokine (C-C motif) ligand receptor; ECG = electrocardiogram; HDL = high density lipoprotein; hsCRP = heat shock C-reactive protein; IL = interleukin; LDL = low density lipoprotein; MCP1 = monocyte chemotactic protein-1; TNF-α = tumor necrosis factor-alpha.
[a] Interim medical history.
[b] Timings relative to dose administration on Day 1.
[c] In all females. Performed in serum at Screening and in urine at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[d] Symptom-directed physical examination.
[e] Body weight only.
[f] In all females.

Table 3: Schedule of Assessments – Part C (Multiple Dose in Subjects with Suspected NASH and Liver Fibrosis)

Study Procedures	Screening	Day -1	Days 1 to 43	Follow-up (5-7 days Post-Final Dose)
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Demographic data	X			
Medical history	X	X[a]		
Urinary drug screen	X	X		
Alcohol breath test	X	X		
Serology	X			
Pregnancy test[c]	X	X		X
Follicle-stimulating hormone	X[i]			
Height and body weight	X	X[g]		X[g]
Fibroscan CAP or Ultrasound[e]	X			
Site staff to query alcohol consumption prior to site visits[f]			At each site visit	X
Study residency:				
Check-in		X	Day 41	
Check-out			Day 2 and Day 43 (24 hours post-final dose)	
Nonresidential visit	X		Days 7, 14, 21, 28, and 35	X
Study drug administration:				
GB1211 or placebo			Days 1 to 41 (0 and 12 hour) and Day 42 (0 hour)[b]	
Pharmacokinetics:				
Blood sampling			Day 1: pre-am dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-am dose Day 2: pre-am dose (24 hours post Day 1 am dose) Day 42: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours post-final dose Day 43: 24 hours post-final dose	

Table 3: Schedule of Assessments – Part C (Multiple Dose in Subjects with Suspected NASH and Liver Fibrosis)

Study Procedures	Screening	Day -1	Days 1 to 43	Follow-up (5-7 days Post-Final Dose)
Exploratory biomarker assessments:				
Serum galectin-3			Day 1: pre-am dose Day 14, 28, and 42[h]	
Fasting glucose and insulin			Day 1: pre-am dose Days 14, 28, and 42[h]	
Lipid profile (eg, LDL, HDL, total cholesterol, and triglycerides)			Day 1: pre-am dose Days 14, 28, and 42[h]	
hsCRP, IL-12, TNF-α, MCP-1, and proinflammatory chemokines (CCL2, CCL3, CCL4, and the chemokine receptors CCR1 and CCR2); and other biomarkers of inflammation as required			Day 1: pre-am dose Day 42[h]	
Exploratory biomarkers of fibrosis (including but not limited to extracellular matrix proteins [TIMP-1, HA, and P3NP], A9, ELF panel, CK18, PAI-1, CH3L1, IL6, pro-collagen 3)			Day 1: pre-am dose Day 42[h]	
Safety and tolerability:				
Adverse event recording	X	X	Ongoing	X
Prior/concomitant medication monitoring	X	X	Ongoing	X

Table 3: Schedule of Assessments – Part C (Multiple Dose in Subjects with Suspected NASH and Liver Fibrosis)

Study Procedures	Screening	Day -1	Days 1 to 43	Follow-up (5-7 days Post-Final Dose)
Clinical laboratory evaluations (including HbA1c and coagulation profile)	X	X	Day 14 and Day 28: pre-am dose Day 43: 24 hours post-final dose	X
Vital sign measurements (blood pressure, pulse rate, and oral body temperature)	X		Day 1: pre-am dose, 4, and 8 hours post-am dose Day 2: pre-am dose Days 7, 14, 21, 28, and 35 Day 42: predose, 4, 8 hours post-final dose Day 43: 24 hours post-final dose	X
12-lead ECG	X		Day 1: pre-am dose and 4 hours post-am dose Days 14 and 28 Day 42: predose, 4 hours post-final dose Day 43: 24 hours post-final dose	X
Physical examination	X	X[d]	Day 1[d]	X[d]

Abbreviations: CAP = Controlled Attenuation Parameter; CCL = chemokine (C-C motif) ligand; CCR = chemokine (C-C motif) ligand receptor; CH3L1 = chitinase-3 like protein-1; CK18 = cytokeratin 18; ECG = electrocardiogram; ELF = E74-like transcription factors; HA = hyaluronic acid; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; hsCRP = heat shock C-reactive protein; IL = interleukin; LDL = low density lipoprotein; MCP1 = monocyte chemotactic protein-1; P3NP = aminoterminal peptide of pro-collagen III; PAI-1 = plasminogen activator inhibitor-1; NASH = nonalcoholic steatohepatitis; TIMP-1 = tissue inhibitor of matrix metalloproteinase-1; TNF-α = tumor necrosis factor-alpha.

[a] Interim medical history.

[b] Timings relative to dose administration on Day 1.

[c] In all females. Performed in serum at Screening and in urine at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

[d] Symptom-directed physical examination.

[e] Fibroscan only to be performed in subjects who do not have documented history of fatty liver.

[f] Site to query whether subject has consumed alcohol within 36 hours of the site visit; and whether alcohol consumption has been limited to 2 units per day on all other days of study. Protocol deviations to be recorded if subject has not.

[g] Body weight only.

[h] Post dosing samples for biomarkers should be collected at approximately the same time each visit.

[i] In all females.