TITLE PAGE

Division: Worldwide Development
Information Type: Clinical Protocol

Title:	An open-label, randomised, single dose, three-way crossover, six sequence, pilot study to determine the relative bioavailability of mosapride 5mg from two candidate formulations of GR107719B relative to one 5mg tablet of reference mosapride citrate (Gasmotin) in healthy adult human subjects under fasting conditions

Compound Number: GR107719B

Effective Date: 06-SEP-2013

SYNOPSIS:

This study aims to determine the relative bioavailability of two candidate formulations of mosapride citrate 5mg tablets compared the reference product Gasmotin (mosapride citrate 5mg) from Dainippon Pharmaceutical Company in healthy adult subjects. This will be an open-label, randomised, single dose, three-way crossover, six sequence study. Subjects will receive a single oral dose separated by at least 7 days and no greater than 14 days washout period. Blood samples for pharmacokinetic analysis will be taken at regular intervals after dosing. Safety will be assessed by measurement of vital signs (blood pressure, body temperature, respiration rate and pulse rate), clinical laboratory assessments, electrocardiogram measurements and review of adverse events. The study will enrol 18 healthy subjects to ensure that 14 complete the study as planned.

Subject: Mosapride citrate anhydrous, Dyspepsia, Bioequivalence, Healthy adult human subjects.

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SPONSOR SIGNATORY:

[redacted] 6 Sept 13

Date

Director, Product Development
Emerging Markets Research and Development
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SPONSOR/MEDICAL MONITOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): N/A

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
%AUCex	Percentage of AUC(0-∞) obtained by extrapolation
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
BA	Bioavailability
BE	Bioequivalence
BMI	Body mass index
BP	Blood pressure
BPM	Beat Per Minute
BUN	Blood urea nitrogen
CI	Confidence Interval
Cmax	Maximum observed concentration
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacokinetics Modelling & Simulation
CPSR	Clinical Pharmacology Study Report
CP-RAP	Clinical Pharmacology Reporting and Analysis Plan
CRF	Case Report Form
DBP	Diastolic blood pressure
DCGI	Drug Controller General of India
DMPK	Drug Metabolism and Pharmacokinetics
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilence
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GORD	Gastroesophageal Reflux Disease
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HR	Heart rate
IB	Investigator's Brochure
IBS	Irritable Bowel Syndrome
ICH	International Conference on Harmonization of Technical

	Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IP	Investigational Product
IRB	Institutional Review Board
Kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LFTs	Liver function tests
µg	Microgram
µL	Microliter
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Milliseconds
PD	Pharmacodynamic
PPDS	Piramal Pharmaceutical Development Services
PK	Pharmacokinetic
QTcF	QT duration corrected for heart rate by Fridericia's formula
QSI	Quantitative Sciences India
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SAS	Statistical Analysis Software
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPM	Study Procedures Manual
SUSAR	Suspected, Unexpected, Serious Adverse drug Reaction
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
tmax	Time of occurrence of Cmax
UFC	Urine free cortisol
ULN	Upper limit of normal
UK	United Kingdom
US	United States
WBC	White blood cells

Trademark Information

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1. INTRODUCTION

Mosapride citrate is a selective 5-HT4 receptor agonist. It is considered a gastroprokinetic agent, stimulating serotonin 5-HT4 receptors in the gastrointestinal nerve plexus, which increases the release of acetylcholine. The elevated levels of acetylcholine results in the enhancement of gastrointestinal motility and gastric emptying [Curran, 2008].

Mosapride citrate products are available in a number of countries worldwide. The therapeutic efficacy for mosapride citrate has been supported by large and well-controlled studies [Mizuta, 2006]. It is indicated to treat gastrointestinal symptoms associated with functional dyspepsia (chronic gastritis), heartburn, nausea, vomiting and acid reflux [Bhan, 2011].

Clinical studies have demonstrated that treatment with mosapride citrate can improve gastric emptying. Clinical pharmacology tests for gastric emptying in healthy adults and patients with chronic gastritis, have found that a single administration of mosapride citrate at 5 mg enhanced gastric emptying [Sakashita, 1993]. Furthermore, the plasma concentration profiles were found to have no significant differences when this drug was given in multiple or single oral doses to healthy male volunteers [Sakashita, 1993]. Therefore, single oral doses of mosapride citrate have been found to be adequate in alleviating gastrointestinal disorders. It is generally well tolerated with diarrhoea, dry mouth, malaise and headchache reported in <5% of patients [Dainippon Pharmaceutical Co., Ltd Gasmotin: mosapride citrate preparation. Prescribing information. Osaka, 2011].

A mosapride citrate tablet developed by Laboratorios Phoenix in Argentina is in the process of reformulation, the reformulation work is being undertaken by Piramal Pharmaceutical Development Services (PPDS), India. This pilot study will investigate the relative bioavailability of two candidate 5mg mosapride citrate tablet formulations compared with the reference product Gasmotin (mosapride citrate 5mg) from Dainippon Pharmaceutical Company in healthy human subjects.

1.1. Study Rationale

This study is required to select a candidate mosapride citrate (GR107719B) formulation for further development and provide data to allow the design of a future pivotal BE study. The candidate formulations will be compared with the innovator Gasmotin (Dainippon Pharmaceutical Company).

The formulation to be taken forward will be chosen primarily on the basis of the Test/Reference ratios and CIs for Cmax (rate of absorption) and AUC (extent of absorption) for the two candidate formulations. The ideal formulation would have Test/Reference ratios close to unity indicating a good match with the reference product and similar or lower within subject variability than the reference product (indicated by a narrow CI, allowing for sample size). Should both candidate formulations show a positive BE a decision on which formulation to progress further will be made based the manufacturability (cost, availability of equipment needed, etc.) and stability of the formulations.

1.2. Brief Background

Dyspepsia is a chronic, recurrent condition that affects the upper abdomen characterized by symptoms of heart burn, indigestion, nausea, bloating, early satiety and upper abdominal fullness [Talley, 2005]. Dyspepsia is considered a common problem worldwide and is frequently associated with gastroesophageal reflux disease (GORD) or chronic gastritis. There is often an associated overlap in symptoms with other common gastrointestinal (GI) disorders, such as irritable bowel syndrome (IBS) and non-erosive reflux disease, making diagnosis and treatment management plans challenging as symptoms may fluctuate and intermittently occur over time [Saad, 2006]. Patients with dyspepsia are diagnosed based on their age, other alarm symptoms (such as dysphagia, vomiting, weight loss, anaemia and GI bleeding) with review by endoscopy. The prevalence of dyspepsia is approximately 15% of the general population in western countries [Saad, 2006].

Treatment

Traditional treatment strategies for dyspepsia and GI disorders include a wide variety of strategies including dietary and lifestyle modifications, antacids, mucosal protectants, antisecretory agents, prokinetics, H. *pylori* eradication, antidepressants and complementary and alternative medical therapies [Saad, 2006].

Mosapride citrate has been demonstrated to be effective in improving GI disorders, chronic gastritis, reflux and dyspepsia. The prokinetic action of mosapride citrate alleviates overall symptoms by shortening the gastric emptying time in patients with GI disorders [Curran, 2008]. Mosapride citrate is considered advantageous for treatment of dyspepsia compared to other prokinetic agents based on tolerability profiles and lower daily dosage units administered [Bhan, 2011]. Furthermore, mosapride citrate has no effects on plasma levels of hormones (prolactin, leutinizing hormone, estradiol and testosterone) and has little effect on K^+ channels and cardiac parameters [Bhan, 2011; Curran, 2008].

Mosapride citrate Pharmacokinetic Profile

After oral administration, mosapride citrate peak plasma concentrations are reached within 0.5 to 1 hour [Sakashita, 1993]. The time to maximum concentration (t_{max}) was found to be 0.6 hours in a fasted state after a single dose of 10mg mosapride citrate [Sakashita, 1993]. Mosapride citrate is primarily metabolised in the liver by cytochrome P450 3A4 to an active metabolite and excreted via urine and faeces with a terminal half life of about 1.5 to 2 hours [Sakashita, 1993, Dainippon Pharmaceutical Co., Ltd Gasmotin: mosapride citrate preparation. Prescribing information. Osaka, 2011]. The pharmacokinetic profiles of mosapride administered as single or multiple doses were found to be generally similar [Sakashita, 1993]. Similarly, no significant differences in the pharmacokinetic profiles between elderly volunteers (aged 65-72 years) and younger volunteers (aged 20-27) when mosapride citrate was administered as single dose [Curran, 2008]. Steady state plasma levels of mosapride are reached after day 2 of consecutive multiple daily dosing [Sakashita, 1993].

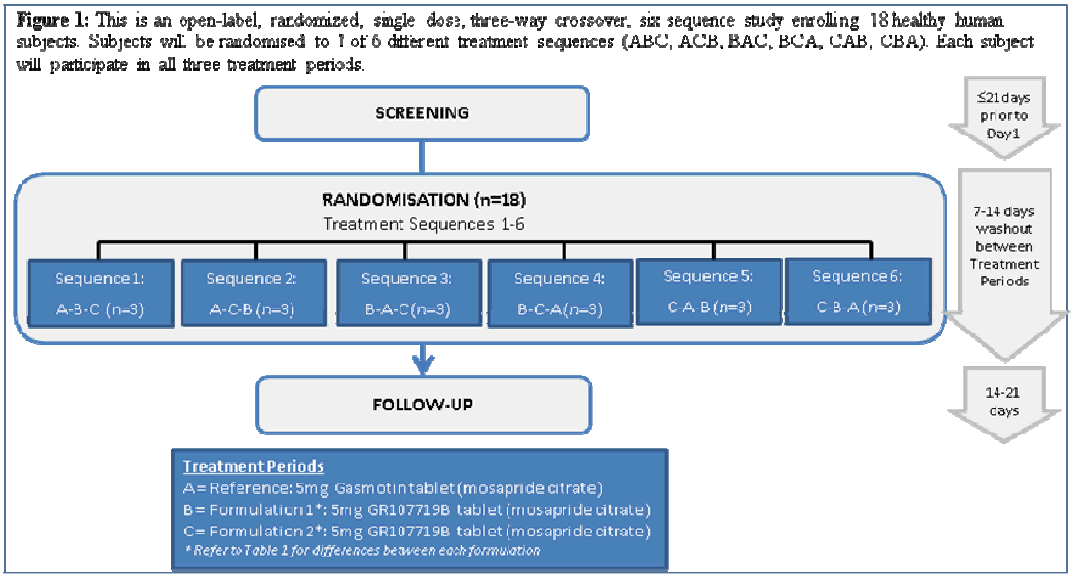
2. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
To characterise the relative bioavailability of mosapride following administration of two candidate tablet formulations of mosapride citrate (GR107719B; 5mg) relative to reference mosapride citrate (Gasmotin; 5mg) in healthy human subjects under fasting conditions.	Plasma PK parameters: Cmax, AUC(0-∞) and AUC(0-t) for mosapride citrate in relevant treatments
Secondary	
To characterise secondary PK parameters of two candidate tablet formulations of mosapride citrate (GR107719B; 5mg) relative to reference mosapride citrate tablets (Gasmotin; 5mg) in healthy human subjects under fasting conditions.	Plasma PK parameters: t_{max}, %AUCex and t½
To monitor the safety and tolerability following administration of two candidate tablet formulations of mosapride citrate (GR107719B; 5mg) compared to reference mosapride citrate (Gasmotin; 5mg) in healthy human subjects under fasting conditions.	Safety and tolerability of all treatments as assessed by blood pressure and pulse rate measurements, review of adverse events and clinical laboratory safety data.

3. STUDY DESIGN

3.1. Study Schematic

Figure 1



3.2. Study Design Detail

This is an open-label, randomised, single dose, three-way crossover, six sequence study enrolling 18 healthy human subjects to ensure at least 14 subjects complete the study as planned. Each subject will participate in all three treatment periods.

All subjects will attend a screening visit within 21 days of their first dosing period (Day 1). Each subject will be admitted to the clinical unit on the evening of Day -1 (i.e. one day before dosing) when entry criteria will be confirmed, including clinical lab safety samples (such that results are available prior to dosing). Subjects will fast overnight and on Day 1 of the first treatment period, all subjects will remain fasted until at least 4 hours after dose administration.

In each treatment period (Day 1), under the supervision of clinic staff, subjects will be randomised to one of six sequences and administered one of the three treatments, A, B or C, as per the randomisation schedule (refer to study schematic in Section 3.1). Subjects will receive a single 5mg tablet of GR107719B (Treatment B / Treatment C) or reference mosapride citrate (Treatment A) administered orally with 240mL of water. Subjects will remain the clinical unit until completion of all assessments at 24 hours post-dose on Day 2, including the collection of the 24 hour post-dose PK sample.

The three treatment periods will be separated by a washout period of at least 7 days and no more than 14 days to ensure the mosapride has been effectively eliminated from the subject between dosing occasions. It is anticipated that dosing will occur weekly however should an individual require a full 14-days between treatment periods then safety labs will be required before dosing. The washout period will be calculated from day of dosing (Day 1) to the subsequent day of dosing (Day 1) in the following Treatment Period.

For subsequent Treatment Periods, all subjects will be admitted to the clinical unit in the evening before dosing (Day -1). Subjects will fast overnight and on Day 1 of each treatment period, subjects will remain fasted until at least 4 hours after dose administration. Subjects will receive a single 5mg tablet of GR107719B (Treatment B / Treatment C) or reference mosapride citrate (Treatment A) administered orally with 240mL of water. Upon completion of the last dosing period (Treatment Period 3), or early withdrawal, subjects will return to the clinical unit within 14-21 days for a Follow-up visit.

All subjects will receive the below mentioned three treatments administered orally in a fasting state:

- (A): Reference Treatment: 5mg Gasmotin (mosapride citrate; Dainippon Pharmaceutical Company)
- (B): Formulation 1: Test Treatment of 5mg GR107719B (mosapride citrate; PPDS);
- (C): Formulation 2: Test Treatment of 5mg GR107719B (mosapride citrate; PPDS);

The order in which the treatments are administered will be in accordance with the randomization schedule. All treatments will be administered with 240mL of water.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the Piramal Clinical Research (PCR) personnel with administrative and detailed technical information that does not impact subject safety.

Table 1

	Dosage	**Number of tablets**	**Description**
Treatment	(A) Reference Treatment: 5 mg mosapride citrate	1 x 5 mg mosapride citrate	Commercially sourced mosapride citrate (Gasmotin) from Dainippon Pharmaceutical Company, Japan
	(B) Formulation 1: Test Treatment 5 mg mosapride citrate	1 x 5 mg mosapride citrate	GR107719B 5 mg mosapride citrate immediate release tablet Test Formulation 1 (L-HPC disintegrant) from Piramal Pharmaceutical Development Services, India
	(C) Formulation 2: Test Treatment 5 mg mosapride citrate	1 x 5 mg mosapride citrate	GR107719B 5mg mosapride citrate immediate release tablet Test Formulation 2 from Piramal Pharmaceutical Development Services, India

3.3. Discussion of Study Design

3.3.1. Design Rationale

The study is a standard single dose fasted bioequivalence design. It is a pilot study and hence is not powered, but in all other respects meets guidelines for all major regulatory authorities on bioequivalence study design.

3.3.2. Dose Rationale

The oral dose proposed for the study of 5mg mosapride citrate is approved for the drug and strength at which these drugs are marketed as, for example, Gasmotin for the treatment of chronic gastritis.

3.4. Risk Management

Refer to the Product Information label for mosapride citrate (Gasmotin) for more information on warnings, precautions, contraindications, adverse events, and other pertinent information on the study treatments, as well as PK, product metabolism and PD.

Mosapride citrate (Gasmotin) is an approved drug in several Asian countries, including Japan, Thailand, Indonesia and the Philippines. Mosapride has a well established safety profile and is approved for the management of gastrointestinal symptoms associated with functional dyspepsia (chronic gastritis), heartburn, nausea and vomiting at the doses similar to be used in the current study. In addition in healthy subjects, mosapride was found to be safe when given as single doses of 2-40mg, 20mg TDS for one day and 10mg TDS for seven days [Nomiyama, 1990]. Although the test mosapride citrate tablets (GR107719B) have not previously been studied, routine monitoring, as described in Section 5.3, Stopping Safety Criteria, Section 6 Study Assessments and Procedures and Section 7.1 Adverse Events and Serious Adverse Events, is considered sufficient risk management.

4. STUDY POPULATION

4.1. Number of Subjects

Eighteen (18) subjects will be enrolled. Each subject will participate in all three treatment periods. Three subjects will be randomised in each of the six sequence options. If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

4.2. Eligibility Criteria

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male and females aged between 18 and 65 years of age inclusive, at the time of signing the informed consent.
2. Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the Investigator in consultation with the GSK Medical Monitor if required agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
3. Body weight ≥ 50 kg and BMI within the range 19 – 24.9 kg/m2 (inclusive).
4. A female subject is eligible to participate if she is of:

- Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy for this definition, “documented” refers to the outcome of the investigator's/designee’s review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records]; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MlU/ml and estradiol < 40 pg/ml (<147 pmol/L) is confirmatory]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods in Section 4.3.1 if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on

the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

- Child-bearing potential with negative pregnancy test as determined by serum hCG test at screening or prior to dosing AND
- Agrees to use one of the contraception methods listed in Section 4.3.1 for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until the follow-up contact visit.
- OR has only same-sex partners, when this is her preferred and usual lifestyle.

5. Male subjects with female partners of child-bearing potential must agree to use one of the contraception methods listed in Section 4.3.1. This criterion must be followed from the time of the first dose of study medication until the follow-up contact visit.
6. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form
7. ALT, alkaline phosphatase and bilirubin ≤ 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
8. Based on single or averaged QTc values of triplicate ECGs obtained over a brief recording period:
    - QTcF < 450 msec

4.2.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

4.2.2.1. Criteria Based Upon Medical Histories

1. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
2. History of regular alcohol consumption within 6 months of the study defined as:
    - An average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (100 ml) of wine or 1 (25 ml) measure of spirits.
3. History of sensitivity to heparin or heparin-induced thrombocytopenia.
4. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.
5. Gastrointestinal disease or with gastrointestinal surgical history which can affect the absorption of the investigational product.

4.2.2.2. Criteria Based Upon Diagnostic Assessments

6. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening
7. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening.
8. A positive pre-study drug/alcohol screen.
9. A positive test for HIV antibody.
10. Pregnant females as determined by positive serum hCG test at screening or prior to dosing.

4.2.2.3. Other Criteria

11. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 90 day period.
12. Lactating females.
13. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 90 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
14. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

4.3. Lifestyle And / or Dietary Restrictions

4.3.1. Contraception Requirements

4.3.1.1. Female Subjects

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%. Female subjects of childbearing potential with same sex partners (when this is their preferred and usual lifestyle) are not required to be abstinent or to use contraception.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of < 1%

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of etonogestrel or levonorgestrel
- Estrogenic vaginal ring

- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label
- **Documented** male partner sterilization prior to **the female subject's entry** into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, cream or suppository).

NOTE: These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

4.3.1.2. Male Subjects

Male subjects with female partners of child-bearing potential must use one of the following contraceptive methods after the first dose of study treatment and until the follow-up contact.

- Condom plus partner use of a highly effective contraceptive (see list in Section 4.3.1.1).
- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

4.3.2. Meals and Dietary Restrictions

- Refrain from consumption of red wine, seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study medication until after the final dose.

4.3.3. Caffeine, Alcohol, and Tobacco

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, chocolate) for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each session.
- During each dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each session.
- Use of tobacco products is not allowed from screening and until after the final follow-up visit.

4.3.4. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

4.4. Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at PCR but will not be transmitted to GSK.

4.5. Withdrawal Criteria and Procedures

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study.

These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the CRF.

Refer to Section 5.3 for subject stopping criteria including Liver Chemistry and QTc.

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). See Section 5.3.1 for details.

4.6. Subject Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit.

5. STUDY TREATMENT

5.1. Investigational Product and Other Study Treatment

	Study Treatment	
Product name:	GR107719B	Gasmotin
Formulation description:	Formulation 1) L-HPC disintegrant Caplet shaped tablet, embossed and film-coated. Formulation 2) Caplet shaped tablet, embossed and film-coated	Caplet shaped tablet embossed with P218 and film-coated
Dosage form:	Tablet	
Unit dose strength(s)/Dosage level(s):	5 mg	
Route/ Administration/ Duration:	Route: Oral Duration: Single dose	
Dosing instructions:	Administer with approximately 240mL of water	
Physical description:	White	White and scored
Manufacturer/ source of procurement:	Piramal Pharmaceutical Development Services, India	Dainippon Pharmaceutical Company, Japan
Method for individualizing dosage:	One tablet to be taken	

5.2. Treatment Assignment

Subjects will be assigned to one of the six treatment sequences and will participate in all three treatment periods as outlined in Table 1 and Figure 1, in accordance with the randomization schedule generated by SAS Version 9.2, prior to the start of the study.

A description of each regimen is provided in the table below:

Table 1 Description of each treatment sequence:

Sequence	No of Subjects per sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3
1	3	A	B	C
2	3	A	C	B
3	3	B	A	C
4	3	B	C	A
5	3	C	A	B
6	3	C	B	A

- (A) Reference Treatment: 5mg Gasmotin (mosapride citrate);
- (B) Test Treatment of 5mg GR107719B (mosapride citrate, L-HPC disintegrant);
- (C) Test Treatment of 5mg GR107719B (mosapride citrate)

Each subject will be assigned a randomization number before receiving their first dose of study medication. The randomization numbers will be assigned in the sequential order starting with the lowest number first. Once a randomisation number has been assigned to a subject it cannot be reassigned to another subject. Subjects who are withdrawn may be replaced if necessary to obtain the required number of evaluable subjects.

5.3. Stopping Criteria

5.3.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Study treatment will be stopped **for a subject** if the following liver chemistry stopping criteria is met:

- ALT ≥ 3xULN

NOTE: Refer to Appendix 1 for details of the required assessments if a subject meets the above criteria**.**

5.3.2. QTc Withdrawal Criteria

A subject that meets either criterion below will be withdrawn from the study. The same QT correction formula (QTcF) should be used to determine inclusion and discontinuation for any individual subject throughout the study.

- QTcF > 500 msec
- Change from baseline: QTc >60 msec

If a subject has underlying bundle branch block the following withdrawal criteria should be used instead:

Baseline QTc value (with underlying bundle branch	QTc withdrawal criteria
<450 msec	>500 msec
450-480 msec	>530 msec

Withdrawal of subjects is to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study

5.3.3. Stopping Safety Criteria

For an individual study participant, stopping criteria include, but are not limited to:

Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g. ECG, vital signs, laboratory tests, etc), as judged by the Principal Investigator in consultation with the Medical Monitor if necessary.

5.4. Blinding

This will be an open-label study.

5.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

5.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

Study treatment must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study treatment. Only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure area with access limited to the investigator and authorized site staff. Study treatment is to be stored at room temperature not exceeding 25°C (77°F) and is to be protected from light. Maintenance of a temperature log (manual or automated) is required.

The investigator and designee (pharmacist) are responsible for study treatment accountability, reconciliation, and record maintenance. The investigator, or designated site staff (e.g., Pharmacist) must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to GSK and the amount supplied and/or administered to subjects. The required accountability unit for this study will be bottles or blister packs and tablets. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study treatment are listed in the SPM.

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

5.7. Assessment of Compliance

When subjects are dosed at the study site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study staff other than the person administering the study treatment. Study site personnel will examine each subject's mouth to ensure that the study treatment was ingested.

5.8. Treatment of Study Treatment Overdose

GSK does not recommend specific treatment for an overdose. The investigator or physician in charge of the subject at the time will use clinical judgment to treat any overdose.

5.9. Treatment After the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because only healthy adult human subjects are eligible for study participation.

5.10. Concomitant Medications and Non-Drug Therapies

5.10.1. Permitted Medications

Paracetamol at doses of ≤2 grams/day is permitted for use any time during the study. Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

5.10.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 6.1. Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

The timing and number of planned study assessments, including safety and pharmacokinetic, assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form. No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

6.1. Time and Events Table

Procedure	Screening (up to 21 days prior to Day 1)	Study Day (each dosing session)																				Follow-up 14-21 (days post-last dose)
			Day 1																			
		Day -1	Pre dose	0h	0.25h	0.5h	0.75h	1h	1.33h	1.67h	2h	2.5h	3h	4h	6h	8h	10h	12h	13 h	16h	24h	
Admission to Unit		X[1]																				
Review of Eligibility Criteria	X		X																			
Informed Consent/ Demographics/ Exam/Medical, Medication, Drug, Alcohol History	X																					
Full Physical	X																					
Brief physical exam		X[2]																				X
Demographics	X																					
12-lead ECG[3, 4]	X		X[3]					X						X				X			X	X
Vital signs[4, 5]	X		X[5]					X			X			X		X		X			X	X
Urine cotinine		X																				
Urine Drug/ Alcohol breath test		X																				
Serum β-hCG (women)	X																					X
Urine β-hCG (women)		X																				
HIV, Hep B and Hep C screen	X																					
Hema/Chem/Urinalysis tests[6]	X	X																			X	X
Meal[7]														X		X			X			
Study treatment dosing[8]				X																		
PK Samples[4]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
AE/SAE Review[9]	<----------																					---------->
Concomitant Medication Review[9]	<----------																					---------->
Discharge																					X	
Outpatient Visit[10]	X																				X	X

1. Subjects will remain in residence at the clinical unit up to 24 hr after dose in each study period. After the collection of the 24 hr blood sample and a safety assessment (vital signs, AE, etc...) they will be checked out by the clinical unit and will return for subsequent treatment periods. The physician may require the subject to stay longer at the clinical unit if deemed necessary for the subject's safety.
2. A Brief Physical Exam may be collected at either Day -1 or Day 1 pre-dose.
3. Baseline for ECG will be defined as the mean of three measurements pre-dose on Day 1. All results must be reviewed by a physician prior to dosing on Day 1. Additional ECG and vital sign measurements may be collected as deemed necessary by the Investigator.
4. Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.
5. Baseline for Vitals will be defined as the average of the last two blood pressure and pulse readings pre-dose on Day 1. All results must be reviewed by a physician prior to dosing on Day 1. Vital sign measurements to be measured in supine position after 5 minutes rest will include systolic and diastolic blood pressure and pulse rate. Additional assessments may be taken at the discretion of the Investigator.
6. Must be reviewed prior to dosing on day 1. Safety Lab analysis will be performed before treatment periods 1 and 3. Additional safety lab may be collected as deemed necessary at the Investigator discretion. Dosing between Treatment Periods will be separated by at least 7 days and no greater than 14 days washout and it is anticipated that dosing will occur weekly. However should an individual require a full 14-days between washout periods, safety labs will be required before dosing.
7. Subjects will be required to fast for at-least 10 hours prior to dosing and at least 4 hours after dose administration (meals may be served according to clinic's schedule on all other days). Meals will be provided to subjects after the completion of PK sample collection and all assessments.
8. Dosing between Treatment Periods will be separated by a washout of 7-14 days. Subjects will remain in a sitting or semi-supine position for at least 4 hours after dosing on Day 1 of each Treatment Period. Each subject will receive single oral dose of each regimen in the morning and will be supervised in the clinic. Dosing will be in the fasted state.
9. AEs and SAEs will be collected from the start of dosing with Investigational Product and until the follow-up visit. However, any SAEs related to study participation or concomitant medications will be recorded from the time a subject consents to participate in the study and until the follow-up visit.
10. Discharge following the collection of the final PK sample draw and following review by a physician to assess subject safety. Subjects will return to the unit for follow-up 14 to 21 days later.

6.2. Demographic/Medical History Assessments

The following demographic parameters will be captured: gender, race and ethnicity.

Medical/medication/alcohol history will be assessed as related to the eligibility criteria listed in Section 4.2.

6.3. Safety

Planned timepoints for all safety assessments are listed in the Time and Events Table (Section 6.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

6.3.1. Physical Exams

- A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.
- A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

6.3.2. Vital Signs

- Vital sign measurements to be measured in supine position after 5 minutes rest will include systolic and diastolic blood pressure and pulse rate and respiratory rate.

6.3.3. Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.3.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

6.3.4. Clinical Laboratory Assessments

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below. Details for the preparation and shipment of samples will be provided by the local laboratory. Reference ranges for all safety parameters will be provided to the site by the laboratory.

If additional non-protocol specified laboratory assessments are performed at the site's local laboratory and result in a change in subject management or are considered clinical significant by the Investigator (for example SAE or AE or dose modification) the results must be captured and sent to GSK along with other study data as defined in Appendix 3.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Clinical Chemistry

BUN	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose, fasting	Bicarbonate	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein

NOTE: Details of Liver Chemistry Stopping Criteria and Follow-Up Procedures are given in Section 5.3.1.

Routine Urinalysis

Specific gravity
pH, glucose, protein, blood and ketones by dipstick
Microscopic examination (if blood or protein is abnormal)

Other screening tests

HIV
Hepatitis B (HBsAg)
Hepatitis C (Hep C antibody)
Urine β-HCG (in females) at Day-1
Serum β-HCG (in females) at all other visits
FSH and estradiol (as needed in women of non-child bearing potential only)
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).

All laboratory tests with values that are significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

6.4. Pharmacokinetics

6.4.1. Blood Sample Collection

Blood samples for pharmacokinetic analysis of mosapride will be collected at the time points indicated in Section 6.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. Seventeen (17) blood samples (1 x 5 mL) will be collected in pre-labelled K_2EDTA vacutainers for each subject during each period.

Processing, storage and shipping procedures are provided in the Study Procedures Manual (SPM) and Lab Manual.

6.4.2. Sample Analysis

Plasma analysis will be performed under the control of Piramal Clinical Research, the details of which will be included in the Study Procedures Manual. Concentrations of mosapride will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the Study Procedures Manual).

7. ADVERSE EVENTS , SERIOUS ADVERSE EVENTS , PREGNANCY AND MEDICAL DEVICE INCIDENTS

7.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.1.1. Time period for collecting AE and SAE information

AEs will be collected and reported from the start of Study Treatment and until the follow-up contact. Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions CRF.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator would promptly notify GSK.

NOTE: The method of, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3.

7.1.2. Method of Detecting AEs and SAEs

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

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.1.3. Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE **include**:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.).

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.1.4. Definition of Serious Adverse Events

If an event is not an AE per Section 7.1.3, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

An SAE is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be

immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Is associated with liver injury **and** impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

- Refer to Appendix 1 for the required liver chemistry follow-up instructions.

7.1.5. Prompt Reporting of SAEs to GSK

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to GSK within 24 hours. Any follow-up information on a previously reported SAE will also be reported to GSK within 24 hours.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in Appendix 3.

7.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.2. Pregnancy

7.2.1. Time period for collecting pregnancy information

All pregnancies in female subjects and/or female partners of male subjects will be collected after the start of dosing and until the follow-up visit.

7.2.2. Action to be taken if pregnancy occurs

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 7.1.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

7.2.3. Action to be taken if pregnancy occurs in a female partner of a male study subject

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomised to receive study medication. After obtaining the necessary written informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

8. DATA MANAGEMENT

For this study subject data will be collected using PCR defined case report forms and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Original CRFs will be retained by PCR and copies will be sent to GSK. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Hypotheses and Treatment Comparisons

Bioavailability

This study is designed to estimate the relative bioavailability of two test formulations of mosapride citrate 5 mg tablets relative to Gasmotin 5 mg tablets. No formal hypothesis will be tested. For each primary pharmacokinetic endpoint, point estimates and corresponding 90% confidence intervals will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference).

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Based on CVw=40% for Cmax [Keller, 2011], the precision estimate will be 29% with 14 evaluable subjects. So assuming the true ratio is 1, the CI will be within +/-29% of the Point Estimate.

9.2.2. Sample Size Sensitivity

Sample size sensitivity was conducted to assess the precision estimate based on a range of subject numbers and a range of variability estimates. Precision estimates are presented in the table based on sample size of 12-16 and CVw between 35-45% for Cmax.

Cvw%	Precision (1/2 width CI)		
	N=12	N=14	N=16
35%	28%	26%	24%
40%	32%	29%	27%
45%	36%	33%	30%

9.2.3. Sample Size Re-estimation

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

9.3.1. Final Analyses

Safety Population/ All subjects Population

Any subject enrolled into the study who receives at least one dose of study medication will be included in the All Subjects Population. This population will be used for the study population and safety displays.

Pharmacokinetic Parameter Population

The subjects in the 'All Subjects' population who completed at least two of the three periods and have received at least one of the test product (B or C) and reference product (A) will be included in the pharmacokinetic and statistical analysis population

9.3.1.1. Safety Analyses

Safety data will be presented in tabular format and summarized descriptively according to Integrated Data Standards Library (IDSL) standards.

9.3.1.2. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of PCR. Plasma mosapride concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin 6.3. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0-∞)], %AUCex and apparent terminal phase half-life (t1/2) of mosapride.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, Piramal Clinical Research.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Piramal Clinical Research.

Following $\log_e$-transformation, Cmax, AUC(0-t) and AUC(0-∞) will be analyzed using a mixed effects model with fixed effect terms for sequence, treatment and subject within sequence in the model. Point estimates and their associated 90% confidence intervals will be constructed for the differences, test formulations and reference. The point estimates and their associated 90% confidence intervals will then be back-transformed to provide point estimates and 90% confidence intervals for the ratios, μ_{T1}/μ_R and μ_{T2}/μ_R.

Tmax will be summarized descriptively.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favourable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent (and any amendments) to be obtained for each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

Written informed consent must be obtained from each subject prior to participation in the study.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.

- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or PCR staff, as appropriate, in accordance with applicable regulations including GCP, and GSK procedures.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If GSK determines such action is needed, GSK will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform investigators or the head of the medical institution (where applicable) and the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

Following closure of the study, the investigator or the head of PCR must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a

true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at PCR.

PCR will also provide the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Liver Safety Process

Scenario 1 Healthy Volunteer Studies

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 5.3.1:

- Immediately withdraw the subject from study treatment
- Notify the GSK medical monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 7.1.4), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up withdraw the subject from the study unless further safety follow up is required
- Do not restart investigational product
- Refer to the Flow chart for a visual presentation of the procedures listed below.

Safety Follow-Up Procedures for subjects with ALT ≥ 3xULN:

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects with ALT ≥3xULN and total bilirubin ≥2xULN (>35% direct bilirubin); or ALT ≥ 3xULN and INR[1] > 1.5:

- This event is considered an SAE (see Section 7.1.4). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

[1] INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants.

In addition, for <u>all</u> subjects with ALT ≥ 3xULN, every attempt must be made to also obtain the following:

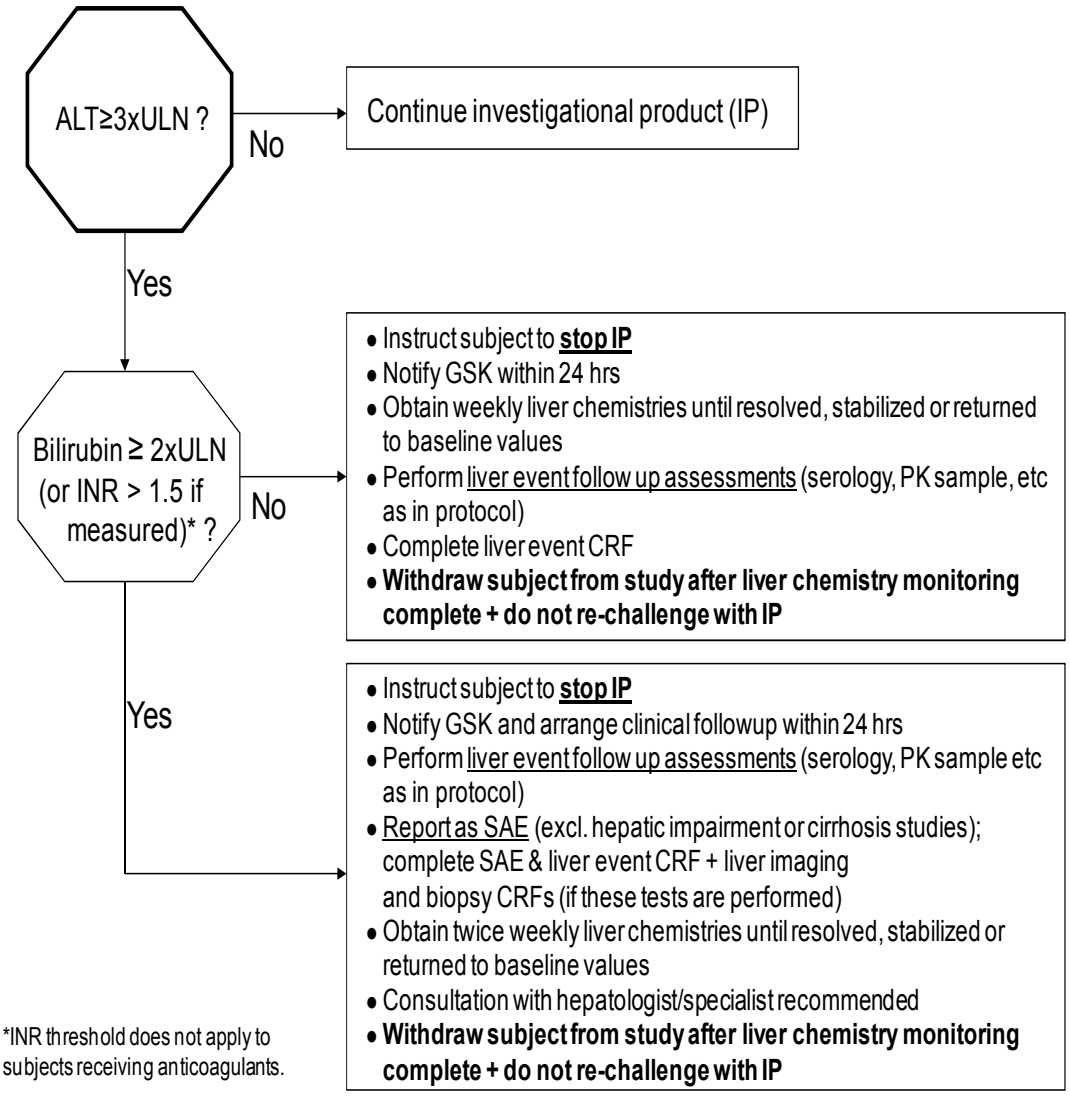
- Viral hepatitis serology including:
  - Hepatitis A IgM antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
  - Hepatitis C RNA.
  - Cytomegalovirus IgM antibody.
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 12h of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose can not be approximated <u>OR</u> a PK sample can not be collected in the time period indicated above, **do not obtain a PK sample**. Instructions for sample handling and shipping are included in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥ 2xULN.
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
- Record alcohol use on the Liver Events CRF.

The following are required for subjects with ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

Refer to the diagram below for a visual presentation of the procedures listed above.



Scenario 2 – Liver Chemistry Stopping Criteria NOT defined in Protocol

The procedures listed below are to be followed if a subject has ALT, bilirubin and/or INR elevations that meet the definition of an SAE (as defined in Section 7.1.4):

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to confirm follow-up.

- Complete the liver event case report forms.
- Upon completion of the safety follow-up withdraw the subject from the study unless further safety follow up is required.
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.
- Obtain viral hepatitis serology including:
    - Hepatitis A IgM antibody.
    - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
    - Hepatitis C RNA.
    - Cytomegalovirus IgM antibody.
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
    - Hepatitis E IgM antibody.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
- Record alcohol use on the Liver Events CRF.
- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week (James LP. Drug Metab Disp 2009; 37:1779–1784). **NOTE: not required in China** Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.
- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

12.2. Appendix 2: Country Specific Requirements

SAE Reporting

In addition to notifying the Sponsor (GSK) of any SAEs as outlined in Section 7 and Appendix 3, the Principle Investigator shall report SAEs to the Drug Controller General of India (DCGI) and to the Chairperson of the IEC within 24 hours, with the minimum SAE information: Study No & molecule Name, event occurred, subject No. name of PI & site etc., duly signed by the investigator with date.

The PI shall take the responsibility of informing and reporting any SAE after due analysis to the following institutions: Licensing Authority, Head CRO, IEC, Expert Committee within 10 calendar days of the occurrence. All responses from the institutions shall be provided to the Sponsor in a timely manner.

Informed Consent:

Informed Consent process will be recorded (audio and video recording) during the study specific ICD presentation and the copy of the recorded tape will be archived along with the study files.

Subject Compensation

The participants will be compensated for the overall inconvenience borne during the study. The Compensation will be paid as per Piramal Clinical Research Internal Current Version of SOP No: CR-CV-08 (Participants Compensation for Participation in a Clinical Study). This will be guided by ICH (International Conference on Harmonization) guidelines and the guidelines issued by CDSCO-DCGI (Central Drugs Standard Control Organization-Drugs Controller General of India)

In case of drop-out/withdrawal of a subject before completion of the study, the amount of compensation is summarized in the table below:

Reasons of withdrawal from the study	Compensation
If participant(s) is withdrawn from the study on medical decision, for his health interest by the attending Medical Officer / Principal Investigator.	Full Compensation
After initiation of the study if participant (s) withdraws on his own free will.	100 % proportionate participation dues
The study is terminated for safety, humanitarian or administrative reasons.	100 % proportionate participation dues
If participant (s) is withdrawn from the study by the Medical Officer / Principal Investigator after signing the Informed Consent Document but before receiving any medications due to participant's violation of requirements of the study or willful misinformation on present and / or past medical illness / history. Also if the participant (s) withdraws after the initiation of the study but before dosing on his own will.	100 % proportionate participation dues

Note 1: In case of an injury occurred during the study, participant will be treated appropriately at Piramal Clinical Research or "well equipped" hospitals such as Care Hospital Nampally, Matrix Hospital, Ramanthapur and Omni Hospitals, Kothapet, and the cost of the medical management shall be borne by PCR.

In the case of an injury occurring to the clinical trial subject, he or she shall be given free medical management as long as required.

In case of the injury occurring to the trial subject is related to the clinical trial such subject shall also be entitled for financial compensation as per order of the Licensing authority and the financial compensation will be over and above any expenses incurred on the medical management.

Incase of death is related to the clinical trial, nominee shall be entitled for 'financial compensation' which is over and above any expenses incurred on medical management.

The quantum of compensation is based on the decision by the Licensing Authority, after receiving the reports from the PCR and Sponsor and also considering the recommendations of the Ethics Committee and Expert committee.

The Sponsor's representative (PCR) whosoever had obtained the permission from the Licensing Authority for conducting the Clinical Trial will pay the compensation in case of trial related injury / death within the receipt of the order.

All the study participants will be covered by an insurance policy i.e. IFFCO-TOKYO General Insurance Co.Ltd (Policy No. [redacted]

12.3. Appendix 3: Procedures for Detection, Evaluation, Follow-Up and Reporting of Adverse Events and Medical Device Incidents

Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the appropriate data collection tool.

It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE data collection tool. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

Subject-completed health outcomes questionnaires and the collection of AE data are independent components of the study. Responses to each question in the health outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed data collection tool. The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Reporting of SAEs to GSK

Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

GSK contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.