TITLE PAGE

Protocol Title: An open-label, randomised, single-dose, two-period cross-over study to evaluate bioequivalence of GR37547 ciprofloxacin 500 mg tablet versus ciprofloxacin 500 mg tablet reference product in healthy adult participants under fasting conditions

Protocol Number: 205730

Short Title: Bioequivalence study between GR37547 500 mg tablet versus ciprofloxacin 500mg tablet reference product in healthy adult participants under fasting conditions.

Compound Number: GR37547

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information

Refer to PAREXEL Communication plan

Regulatory Agency Identifying Number(s):

N/A

Approval Date: 11-APR-2017

SPONSOR SIGNATORY:

PPD

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Classic and Established Products

11/04/2017
Date

PPD

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1. SYNOPSIS

Protocol Title: An open-label, randomised, single-dose, two-period cross-over study to evaluate bioequivalence of GR37547 ciprofloxacin 500 mg tablet versus ciprofloxacin 500mg tablet reference product in healthy adult participants under fasting conditions

Short Title: Bioequivalence study between GR37547 500 mg tablet versus ciprofloxacin 500mg tablet reference product in healthy adult participants under fasting conditions.

Rationale:

This study will determine if ciprofloxacin 500 mg tablets (test formulation: GR37547; CIPVAL™; GlaxoSmithKline Pakistan Limited) are bioequivalent to ciprofloxacin 500 mg tablets (reference formulation: Ciproxin; Bayer Limited, United Kingdom).

Objectives and Endpoints:

Objectives	Endpoints
Primary To determine if 500 mg Ciprofloxacin (GR37547) tablets are bioequivalent to reference 500 mg Ciprofloxacin tablets in healthy adult participants under fasting conditions.	Plasma PK parameters: $AUC_{(0-t)}$ and C_{max}, for ciprofloxacin in relevant treatments.
Secondary To assess secondary PK parameters of 500 mg ciprofloxacin tablets (GR37547) relative to reference 500 mg ciprofloxacin in healthy adult participants under fasting conditions. To compare the safety and tolerability of a single dose of a 500 mg ciprofloxacin tablet (GR37547) with reference 500 mg ciprofloxacin tablet, in healthy adult participants under fasting conditions.	• Plasma PK parameters: $AUC_{(0-\infty)}$, t_{max}, $\%AUC_{ex}$ and $t_{½}$ for ciprofloxacin in relevant treatments. • Adverse events (AE), clinical laboratory values (Haematology and Biochemistry), ECGs and vital signs
$AUC_{(0-\infty)}$ = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; $\%AUC_{ex}$= Percentage of AUC(0-∞) obtained by extrapolation; $AUC_{(0-t)}$= Area under the plasma concentration versus time curve from time zero to t, where t is the time of the last quantifiable concentration; $t_{1/2}$= Terminal phase half-life; Cmax= Maximum observed concentration; Tmax= Time of occurrence of Cmax.	

Overall Design:

This is a Phase I, open label, balanced, randomised, single dose, two-way crossover study, enrolling 26 healthy participants at a single centre.

Each enrolled study participant will take part in two treatment periods in accordance with the randomisation schedule. The treatment periods will be separated by a washout period of at least 7 days and no more than 14 days.

Number of Participants:

Approximately 26 participants will be randomized to yield at least 22 evaluable participants completing the study.

Treatment Groups and Duration:

The total duration in the study for each participant is expected to be up to approximately 5 - 7 weeks, from screening to their last visit.

Study treatments will be referred to as Test and Reference throughout the protocol:

- **Treatment A – Test: GR37547** (CIPVAL™), ciprofloxacin 500 mg tablets.
- **Treatment B - Reference:** Ciproxin, ciprofloxacin 500 mg tablets.

Treatment Groups and Sequences:

- Participants will be randomised to one of two sequences, and administered a single oral dose of one of the two treatments (A or B) in each treatment period, such that each participant receives a dose of each treatment in the study.

2. SCHEDULE OF ACTIVITIES (SOA)

Details of study assessments and collection windows are given in Table 1

Table 1 Schedule of Activities

Procedure	Screening (Day -21 to Day -1)	Treatment Periods 1 and 2			Follow-up (within approximately 7 days post last dose or at discontinuation)	Notes
		Day –1	Day 1	Day 2		
Informed consent	X					
Inclusion and exclusion criteria	X	X				Refer to Section 6 . Recheck clinical status before randomization. and
Admission to the Unit (domiciled)		X	X	X		Participants to be admitted on Day -1 of each treatment period, and discharged on Day 2.
Outpatient Visits	X					
Discharge				X		Participants will be discharged from the unit after the collection of the 24 hour post dose PK sample, vital signs (VS), lab assessments and, urinalysis; following review by a doctor to assess participant safety. At the end of treatment period 2, in addition to the other assessments taken at 24 hours post dose (Day 2), all participants will also have an ECG and urine pregnancy test (females), prior to discharge. Participants who have normal safety assessment results at the end of treatment period 2 do not require a follow up.

Procedure	Screening (Day -21 to Day -1)	Treatment Periods 1 and 2			Follow-up (within approximately 7 days post last dose or at discontinuation)	Notes
		Day –1	Day 1	Day 2		
Follow up (Phone Call or Outpatient Visit)					X	If a participant's safety assessments (medical exam, VS, ECG, Lab assessments) are abnormal and clinically significant at Treatment Period 2 discharge, then a follow up phone call or outpatient clinic visit is required within 7 days. Enquiries on the participant's general health, including any AEs/SAEs/concomitant medication should be recorded in the medical notes.
Demography and Medical history (includes substance usage)	X					Substances: Drugs, Alcohol, tobacco and caffeine
Full physical examination including height and weight	X	X				Abbreviated physical exam (excluding height and weight) performed at Day -1
Past and current medical conditions	X	X				
Pregnancy test (WOCBP only)	X	X		X		Serum β-hCG: at screening. Urine β-hCG: at Day-1 and at the end of Treatment period 2 on Day 2 .
HIV, Hepatitis B and C screening	X					Testing for Hepatitis B (HBsAg) and Hepatitis C (HepC antibody) at screening is not required if this was performed within 3 months prior to first dose of study treatment. Participants, who are positive for Hepatitis C antibody due to prior resolved disease, must have a confirmatory negative Hepatitis C RNA test.

Procedure	Screening (Day -21 to Day -1)	Treatment Periods 1 and 2			Follow-up (within approximately 7 days post last dose or at discontinuation)	Notes
		Day –1	Day 1	Day 2		
Laboratory assessments (include liver chemistries)	X	X		X		**Screening**: Participants are required to fast at least 10 hours prior to the Screening Laboratory assessment. Haematology, Biochemistry, glucose -6-phosphate dehydrogenase, Coagulation profile (PT and aPTT) and Urinalysis are assessed. **Day -1:** Haematology, Biochemistry and Urinalysis are assessed. **Day 2:** Haematology, Biochemistry and Urinalysis samples are obtained 24 hours post dose, prior to discharge. Additional safety labs must be collected as deemed necessary at the Investigator's discretion.
Urine Drug/Urine Cotinine/Breath alcohol	X	X				
12-lead ECG[a]	X		X	X		12-lead ECG will be completed at: • Screening, • Day 1: ECG 2h post dose (t_{max}) to be completed before vital signs and 2 hour PK sample. • Day 2: at discharge, at the end of Treatment Period 2 prior to the last PK sample • Follow up: only required if the ECG at discharge was abnormal and clinically significant ECGs to be taken ±30min of time points specified

Procedure	Screening (Day -21 to Day -1)	Treatment Periods 1 and 2			Follow-up (within approximately 7 days post last dose or at discontinuation)	Notes
		Day –1	Day 1	Day 2		
Vital signs[a]	X		X	X		Vitals will be taken at: • Screening, • Day 1: pre-dose and post dose at, 2.00, 4.00, and 6.00 hours • Day 2: 24.00 hours post-dose. Post dose vitals to be taken ±30min of each time point.
Randomization			X			Day 1 of treatment period 1 only.
Study treatment			X			Screening and Day -1 results must be reviewed by physician prior to randomisation and dosing. Participants to be fasted 10.00 hours prior and 4.00 hours post dose. Dosing between Treatment periods will be separated by a washout of 7 -14 days. Participants will remain in a sitting or semi-supine position for at least 4 hours after dosing on Day 1 of each treatment period.
AE Review		←==========		==========→		Collected from the start of dosing (Day 1, Treatment period 1) to the participant's final discharge from study at the end of Treatment Period 2, follow up call or last outpatient visit, whichever is the latest.
SAE review	←==========			==========→		Any SAEs assessed as related to study participation (e.g. investigational product, protocol-mandated procedures, invasive tests) or related to a GSK concomitant medication will be recorded from the time a participant consents to participate in the study up to and including any follow up contact.

Procedure	Screening (Day -21 to Day -1)	Treatment Periods 1 and 2			Follow-up (within approximately 7 days post last dose or at discontinuation)	Notes
		Day –1	Day 1	Day 2		
Concomitant medication review	←==========→					
Pharmacokinetics[a]			X	X		**Day 1:** Pre-dose, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.50, 6.00, 8.00, 12.00, 18.00 hours **Day 2:** 24.00 hours post dose Pre-dose sample will be taken within 15 minutes before dose. Post dose samples for: • 0.500 -2.00 hours will be taken ±2 min;, ; • 2.50 – 8.00 hours will be taken ± 5 min; and • 12.00 – 24.00 hours will be taken ± 10 min.

a. The order of assessments to be followed where an ECG, Vital Signs and Blood sample for either PK or Lab assessments are required at the same time point, should always be first ECG, second vital signs and lastly blood sampling, whilst ensuring that the timing for PK blood samples remains within the sampling window.

- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Institutional review board (IRB)/ Independent ethics committee (IEC) and regulatory authority will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).
- AE= Adverse Event; aPTT= Activated Partial Thromboplastin Time; ECG= Electrocardiogram; GSK= GlaxoSmithKline; HIV= Human Immunodeficiency Virus; hr= Hour; IP= Investigational Product; PK= Pharmacokinetic; PT= Prothrombin Time; SAE= Serious adverse event(s)

3. INTRODUCTION

3.1. Study Rationale

GSK Product, GR37547 (Ciprofloxacin) 500 mg tablets is marketed in Pakistan as CIPVAL™. This study is required to determine whether the test product GR37547/CIPVAL™ is bioequivalent to the reference ciprofloxacin 500 mg tablets in healthy adult participants. Bioequivalence (BE) will be declared if the 90% confidence interval (CI) for the true ratio of test to reference geometric means falls entirely within the range of 0.80 to 1.25 for all primary PK parameters.

3.2. Background

Ciprofloxacin is a synthetic fluoroquinolone antibiotic with activity against Gram positive and Gram negative bacteria. Ciprofloxacin exerts its bactericidal effect by inhibition of Topoispmerase II (DNA gyrase) and Topoisomerase IV, thus interfering with bacterial DNA replication, repair, transcription and recombination. The mechanism of action of fluoroquinolones including Ciprofloxacin differs from other antibiotic classes such as penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines therefore, microorganisms resistant to these classes of antibiotics are usually susceptible to fluoroquinolones. The converse applies where microorganisms resistant to Ciprofloaxicin are usually susceptible to the other classes of antibiotics [**APO-CIPROFLOX** Package Insert, 2012].

Indications and Dosing

Ciprofloxacin is used to treat a wide number of infections because of its wide antibacterial spectrum, extensive tissue distribution, prolonged half-life, good oral absorption and lack of cross-resistance with other antibacterials [Morera, 2001].

Ciprofloxacin is indicated for treatment of infections caused by susceptible strains of the causative microorganisms. Factors which determine the dose include the indication, severity, site of the infection and the renal function of the patient. In children and adolescents the body weight is also taken into account. The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course. Doses may range from a single 500 mg dose once off for Gonococcal uretritis and cervicitis, to 750 mg twice daily taken for a maximum of 3 months for bone and joint infections. In some infections or infection sites higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents is required [**CIPROXIN** Package Insert, 2016].

Clinical Pharmacology

Ciprofloxacin tablets dissolve rapidly in the gastrointestinal tract following oral administration, and are absorbed in the duodenum and jejunum. Following oral dosing, the bioavailability of ciprofloxacin is 70-80%. Ciprofloxacin bioavailability was unaltered by food.[Shah, 1999]. Concurrent intake of foods and cations such as iron,

calcium and magnesium result in prolongation of the time to reach peak serum levels [Morera, 2001]. It is therefore recommended that ciprofloxacin should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice [**CIPROXIN** Package Insert, 2016].

Following a 500 mg dose, maximum serum concentrations (C_{max}) ranging between 1.5 to 2.9mg/L, are reached within 1-2 hrs following dosing. [Shah, 1999]. Protein binding is 20-30%, and ciprofloxacin is present in the plasma in a non-ionized form, it diffuses freely into the extravascular space [**CIPROXIN** Package Insert, 2016] . After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions [**CIPRO** Package Insert, 2011].

The total ciprofloxacin area under the serum concentration versus time curve (AUC) increases in proportion to dose. Four metabolites have been reported, in the urine identified as desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). M1 to M3 display antibacterial activity comparable to or inferior to that of nalidixic acid, while M4, with the smallest quantity, is largely equivalent to norfloxacin in its antimicrobial activity. [**APO-CIPROFLOX** Package Insert, 2012].

Ciprofloxacin is an inhibitor of cytochrome P450 1A2 (CYP1A2) mediated metabolism. Clinically significant AEs of any drug metabolized by CYP1A2 can occur if co-administered with ciprofloxacin, due to increased plasma concentrations of the co-administered drug [**CIPRO** Package Insert, 2011]. Co-administration with tizanidine is contra-indicated, since co-administration may increase the serum concentrations of tizanidine leading to tizanidine induced side effects (hypotension, somnolence, drowsiness). Refer to Ciproxin label for products that are contra-indicated.

Ciprofloxacin is predominantly renally excreted with approximately 40 to 50% of an orally administered dose recovered as unchanged drug in the urine with excretion virtually complete within 24 hrs after dosing. Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Approximately 20 to 35% of an oral dose is recovered from the faeces within 5 days after dosing with 1-2% of the dose is recovered from the bile as metabolites. In humans with normal renal function, the serum elimination half life ($t_{½}$) is approximately 4-7 hours. In severely renally impaired subjects the ciprofloxacin half-life is increased up to 12 h [**CIPROXIN** Package Insert, 2016].

A detailed description of the chemistry, pharmacology, efficacy, and safety of ciprofloxacin is provided in the package insert for Ciproxin .

3.3. Benefit/Risk Assessment

Ciprofloxacin was first approved as an antibacterial agent by the Medicines and Healthcare Product Regulatory Agency (MHRA), in the United Kingdom (UK) in 1987 [**CIPROXIN** Package Insert, 2016]. The safety profile of ciprofloxacin is well established based on clinical trial safety data and unsolicited pharmacovigilence reports. More detailed information about the known and expected benefits and risks and reasonably expected AEs of Ciprofloxacin may be found in the Summary of Product Characteristics (SmPC) [**CIPROXIN** Package Insert, 2016].

The following section outlines the risk assessment and mitigation strategy for this protocol.

3.3.1. Risk Assessment

The potential risks of clinical significance for Ciprofloxacin tablets are derived from the prescribing information from marketed formulations during chronic therapeutic use. Most of these reported risks are uncommon, rare or very rare. The likelihood of these risks in a healthy volunteer population receiving a single dose is therefore expected to be lower.

Risks associated when co-administered with other medications are not included as this is an acute dose study in healthy participants.

Table 2 Summary of Risks and Mitigation Strategies for Investigational Products

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GR37547]		
Allergic reactions	Contraindication: Anaphylaxis and anaphylactic shock which may be life threatening may occur if a volunteer has an allergy to the active substance ciprofloxacin, excipients, or other quinolones. Hypersensitivity reactions have been reported following the first dose. Some reactions reported include cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria, and itching. Other hypersensitivity reactions include fever, rash, severe dermatologic reactions (e.g. Stevens-Johnson syndrome); vasculitis; arthralgia; myalgia; serum sickness; or allergic pneumonitis.	Exclude participants with a known history of hypersensitivity to quinolones, ciprofloxacin, or excipients including cellulose microcrystalline, crospovidone, maize starch, magnesium stearate, silica colloidal anhydrous, hypromellose, macrogol and titanium dioxide. Further doses must be discontinued if a participant develops skin rash, jaundice, or any other sign of hypersensitivity following the study medication, and supportive measures immediately instituted. In the event of serious anaphylactic reactions, epinephrine must be given immediately. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as required.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Tendinopathy and Tendon rupture	Warning: Fluoroquinolones, including Ciprofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. Although reports of this adverse reaction (AE) have most frequently involved the Achilles tendon, tendonitis of other sites such rotator cuff (the shoulder), the hand, the biceps, the thumb have also occurred. The risk is higher for older patients (>60 years of age), patients on corticosteroids, patients with rheumatoid arthritis, and those with kidney, heart or lung transplants; however there have been reports of tendonitis in patients with no risk factors. Cases have been reported up to several months after discontinuation of ciprofloxacin therapy.	Only healthy participants ≤60 years of age will be included. Participants will be cautioned to avoid strenuous physical activity during participation in this study.
Photosensitivity reactions	Precaution: Ciprofloxacin may cause photosensitivity /phototoxicity reactions of the skin including exaggerated sunburn reactions (e.g. burning, erythema, exudation, vesicles, blistering and oedema).	Study participants will be advised to avoid direct exposure to sunlight and UV radiation such as sunbeds for 24 hours after dosing.
Safety of Ciprofloxacin has not been established in patients under the age of 18 years, pregnant women and nursing women.	Warning: Ciprofloxacin is excreted in human milk; therefore infants of nursing mothers on ciprofloxacin may be at risk. Damage to juvenile weight-bearing joints and lameness were observed both in rat and dog studies. Permanent lesions of the cartilage were observed on histopathological examination of weight bearing joints of immature dogs.	Exclude participants ≤18 years of age, pregnant women and nursing women. Contraception guidance is provided in the Participant Information Leaflet.
Musculoskeletal reactions and exacerbation of Myasthenia Gravis	Warning: Muscular skeletal pain, and arthralgia may	Only healthy volunteers will be enrolled.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	occur. Rare instances (≥1/10000 <1000) of myalgia, arthritis and increased muscle tone and cramping have been reported. Fluoroquinolones, including ciprofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis with resultant requirement for ventilatory support, or resultant death.	
Prolongation of QT interval	Warning: Ciprofloxacin may cause tachycardia, ventricular arrhythmia or QT interval prolongation in patients with risk factors for QT interval prolongation such as: • the elderly and women, • patients on concomitant medication such as class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics • those with congenital long QT syndrome • uncorrected electrolyte imbalance (hypokalemia and hypomagnesemia) • Cardiac disease (eg.heart failure, myocardial infarction, bradycardia)	Participants older than 60 years of age will be excluded, and those with cardiac disease, electrolye imbalance (Hypokalaemia, hypomagnesaemia), and known risk factors for Torsades des pointes. Only healthy participants will be included. ECG measurements taken during screening and post dose for each period where ciprofloxacin is administered.
Central Nervous System (CNS) Reactions	Warning: Ciprofloxacin could trigger headache, dizziness, tremors, restlessness, sleep disorders or taste disorders. Ciprofloxacin may affect reaction time and thus the ability to drive or operate machinery may be impaired. Rare cases (≥1/10000 to <1/1000) tremor and seizures (including stats epilepticus) have also been	Only healthy volunteers will be included, participants with a history of psychiatric conditions (including depression, anxiety, psychosis) will be excluded. Participants will be advised against driving or operating machinery for 24 hours following the dose of study medication.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	reported. Psychiatric reactions may occur including anxiety, paranoia, depression, confusion, psychoses, hallucinations, depression, nervousness, agitation, insomnia, anxiety, paranoia, nightmares and rarely, suicidal thoughts or acts. Depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted suicide or completed suicide. There have also been very rare cases (<1/10000) of migraine, disturbed coordination, gait disturbance, olfactory nerve disorders, intercranial hypertension and increased intercranial pressure (including pseudotumour cerebri).	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Peripheral Neuropathy	Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin.	Further ciprofloxacin doses will be discontinued if any participant experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.
Vision disorders	Warning: Impaired vision such as diplopia and colour distortions may also occur.	Study participants will be advised to immediately report any signs of visual disturbances to the investigator.
Hearing disorders	Precaution: There have been rare cases of tinnitis, or transitory deafness (especially at higher frequencies) with ciprofloxacin.	Study participants will be advised to immediately report any signs of hearing disturbances to the investigator.
Metabolic reactions	Precaution: Hypoglycaemia can occur in Diabetic patients. Ciprofloxacin may increase the effects of caffeine, and result in caffeine accumulation if consumed concomitantly with quinolones.	Only healthy volunteers to be enrolled. Exclude volunteers with known or suspected Diabetes based on history, and investigator discretion following review of fasting blood glucose results. All participants to be advised to avoid caffeine containing food and beverages for 24 hours prior until 24 hours following dosing with ciprofloxacin.
Gastrointestinal reactions	Warning: Nausea and diarrhoea are the most commonly reported adverse drug reactions with Ciprofloxacin treatment. Cases of painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding and loss of	Participants will be monitored closely, and appropriate therapy initiated immediately if any symptoms appear. Participants will be asked to contact the site if any symptoms appear within 24 hours after discharge.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	appetite has also been reported. Vomiting, abdominal pain, dyspepsia and flatulence although uncommon (≥1/1000 to , 1/100) have been reported. Severe and persistent diarrhoea may occur during or after treatment (including several weeks after treatment). The antibiotic associated colitis could be life threatening with a fatal outcome. Very rare cases of pancreatitis (<1/10000) have been reported.	
Renal and urinary reactions	Warning: Rare Cases (≥1/10000 to <1/1000) of renal failure, crystalluria, haematuria, tubulointerstitial nephritis have been reported.	Healthy participants with normal renal function as determined by review of creatinine clearance, at screening will be enrolled. Participants will be advised to stay well hydrated in the 24 hours following dosing.
Hepatobiliary reactions	Warning: Cases of hepatic necrosis and life threatening hepatic failure have been reported with ciprofloxacin. Patients with previous liver damage may have an increase in transaminases, alkaline phosphatase or cholestatic jaundice.	Participants will be closely monitored for 24 hours following treatment and advised to immediately report any signs and symptoms of hepatic disease such as anorexia, jaundice, dark urine, pruritus or tender abdomen. Laboratory biochemistry results will be reviewed for increases in transaminases, alkaline phosphatase or bilirubin. Any increases to > ULN from baseline levels, following the first dose, will result in discontinuation from further dosing of study treatment based on PI discretion.
Respiratory disorders:	Precautions: dyspnoea, epistaxis, laryngeal or pulmonary oedema, hiccough, haemoptysis, bron-chospasm, pulmonary embolism have occurred in < 1% of patients taking ciprofloxacin.	Participants will be closely monitored for any respiratory disorders and, treatment initiated if indicated.
Blood and Lymphatic system reactions	Eosinophilia, Leukopaenia, anaemia, neutropaenia, leukocytosis and thrombocytopenia may occur	All potential participants will be tested for glucose -6-phosphate dehydrogenase at screening and those

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	following ciprofloxacin. Haemolytic reactions could occur in patients with glucose-6-phosphate dehydrogenase deficiency. Very rare cases (<1/10000) of agranulocytosis, pancytopaenia, and bone marrow depression (life threatening) have been reported.	with values below normal will not be entered into the study. All participants will be examined for clinical signs and laboratory signs of haemolysis, so that immediate treatment can commence. Physical signs of haemolysis include weakness, fatigue, pale skin, fainting, shortness of breath, rapid heart rate and dark urine. All participants will be asked to report any of these immediately. Laboratory signs of haemolytic anaemia include hemoglobinuria, a reduction in red blood cell count and haemoglobin and increase in reticulocyte count, lactate dehydrogenase and bilirubin levels. Post dose haematology results will be reviewed for any other blood abnormalities.
Inhibition of Cytochrome P450 (CYP 450)	Ciprofloxacin is a moderate inhibitor of CYP450 and the CYP1A2 enzyme pathway. Co administration of ciprofloxacin and other medications primarily metabolized via the same metabolic pathways (e.g. theophylline, methylxanthines, tizanidine, cloazpine, duloxetine and also caffeine) results in increased plasma concentrations of the coadministered medications and could lead to clinically significant pharmacodynamic side effects of the coadministered medications.	Healthy volunteer study, with no concomitant treatments, other than those allowed in Section 7.7 during participation in the study, therefore no drug/drug interactions are expected.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Blood sampling	An intravenous cannula will be inserted into participants to obtain blood samples for testing. This may cause some pain, discomfort, bruising and redness/irritation at the site of injection.	Participants will be monitored closely by the site staff during the visits. The cannula will be removed if this is causing pain and discomfort. If the cannula is removed, the subsequent blood samples will be collected by venepuncture or the cannula will be replaced.
Other		
Not applicable	Not applicable	

3.3.2. Benefit Assessment

Participants enrolled into this study are healthy participants. There will be no direct health benefits gained from participation in this study. The participants' involvement will be contributing to the PK analysis and safety profile of GR37547 compared to reference ciprofloxacin tablets.

3.3.3. Overall Benefit: Risk Conclusion

Healthy volunteers will not gain any direct health benefit by participating in this study. Measures have been taken to minimise risk to participants in this study.

4. OBJECTIVES AND ENDPOINTS

Table 3 Study Objectives and Endpoints

Objectives	Endpoints
Primary To determine if 500 mg Ciprofloxacin (GR37547) tablets are bioequivalent to reference 500 mg Ciprofloxacin tablets in healthy adult participants under fasting conditions.	Plasma PK parameters: $AUC_{(0-t)}$ and C_{max}, for ciprofloxacin in relevant treatments.
Secondary To assess secondary PK parameters of 500 mg ciprofloxacin tablets (GR37547) relative to reference 500 mg ciprofloxacin in healthy adult participants under fasting conditions . To compare the safety and tolerability of a single dose of a 500 mg ciprofloxacin tablet (GR37547) with reference 500 mg ciprofloxacin tablet, in healthy adult participants under fasting conditions.	• Plasma PK parameters: $AUC_{(0-\infty)}$, t_{max}, $\%AUC_{ex}$ and $t_{½}$ for ciprofloxacin in relevant treatments. • Adverse events (AE), clinical laboratory values (Haematology and Biochemistry), ECGs and vital signs
$AUC_{(0-\infty)}$ = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; $\%AUC_{ex}$= Percentage of AUC(0-∞) obtained by extrapolation; $AUC_{(0-t)}$= Area under the plasma concentration versus time curve from time zero to t, where t is the time of the last quantifiable concentration; t1/2= Terminal phase half-life Cmax= Maximum observed concentration; Tmax= Time of occurrence of Cmax.	

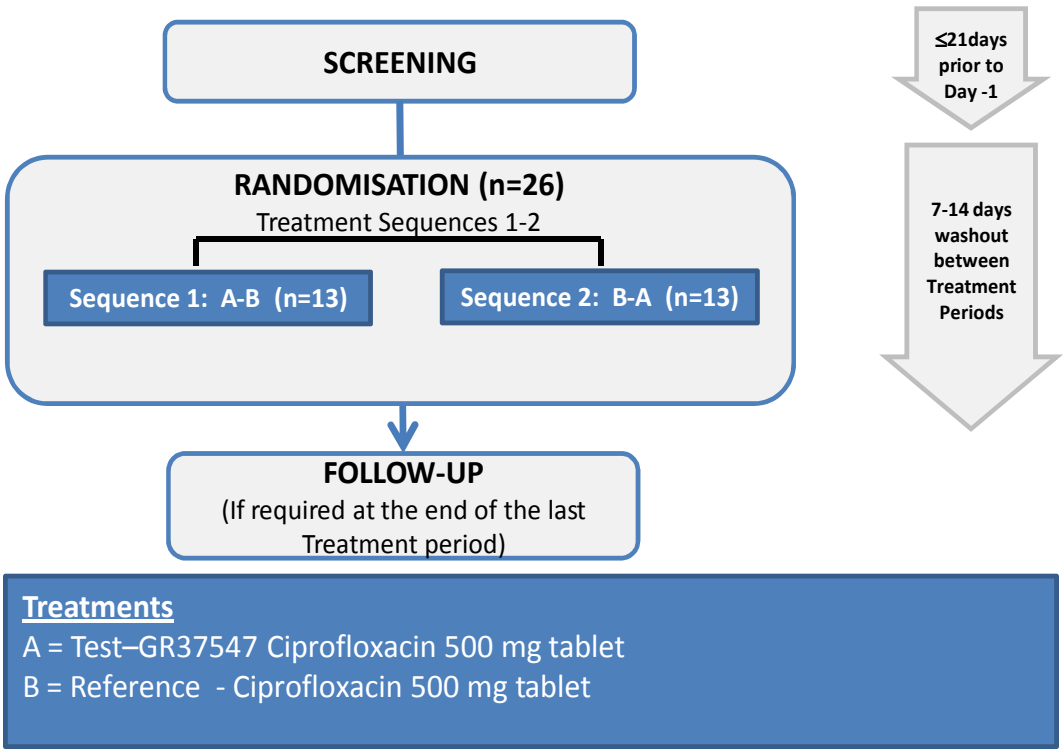
5. STUDY DESIGN

5.1. Overall Design

This is a Phase I, open label, balanced, randomised, single dose, two-way crossover study, enrolling approximately 26 healthy participants at a single centre.

Each enrolled study participant will participate in two treatment periods in accordance with the randomisation schedule. The treatment periods will be separated by a washout period of at least 7 days and no more than 14 days.

Figure 1 Study Schematic



Study participants will be randomised to one of two treatment sequences (A-B or B-A). A single dose of one of the two treatments A or B, will be administered on Day 1, in each treatment period. Each participant will participate in both treatment periods and receive a single dose of each treatment.

Study treatments will be referred to as Test and Reference throughout the protocol:

- **Treatment A – Test: GR37547** (CIPVAL™), ciprofloxacin 500mg tablets.
- **Treatment B - Reference:** Ciproxin, ciprofloxacin 500mg tablets.

Treatment periods 1 and 2 will be separated by a washout period of 7 to 14 days.

The total duration in the study for each participant is expected to be 5 to 7 weeks, from screening to their last visit.

5.2. Number of Participants

Approximately 26 participants will be randomized such that at least 22 evaluable participants complete the study.

Participants who withdraw or are withdrawn from the study will not be replaced, unless fewer complete the study than the estimated number of evaluable participants (see Section 10.1).

If a Participant is replaced, the replacement will be allocated the subject number of PPD plus the subject number being replaced (e.g., Subject PPD will be replaced by PPD The subject numbers being replaced will be selected such that the replacement participants receive the same treatment sequence as the withdrawn participants and the sequence balance is maintained.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial.

5.4. Scientific Rationale for Study Design

- This study is a standard single dose fasted BE design.
- This study will assess whether the test formulation is bioequivalent to the reference treatment.
- This is a pivotal study and meets guidelines for all major authorities on BE study design.

5.5. Dose Justification

The dose of ciprofloxacin (500 mg) in GR37547 is a well established and approved dose, marketed for the treatment of bacterial infections in adults. This study will be conducted using a single dose of the highest GR37547 ciprofloxacin strength marketed, in keeping with international BE guidelines. [EMEA, 2010].

6. STUDY POPULATION

Specific information regarding warnings, precautions, contra-indications, AEs, and other pertinent information on the Test product or other study treatment that may impact participant eligibility is provided in the reference 500 mg ciprofloxacin product information leaflet [**CIPROXIN** Package Insert, 2016].

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted, as these can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety.

Therefore adherence to inclusion and exclusion criteria as stated in the protocol is essential.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be between 18 and 60 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Healthy, non-smoker, as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the normal reference range for the population being studied may be included only if the investigator in consultation with the 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.

Weight

4. Body weight ≥50 kilogram (kg) and body mass index (BMI) within the range 19-30kg/m^2(inclusive).

Sex

5. Healthy Male or female participants

   a. Male participants:

   A male participant must agree to use contraception as detailed in Appendix 1 of this protocol during the treatment period and for at least 5 days, after the last dose of study treatment and refrain from donating sperm during this period.

   b. Female participants:

   A female participant is eligible to participate if she is not pregnant (see Appendix 1), not breastfeeding, and at least one of the following conditions applies:

   (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 1

OR

(ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 1 Appendix 5 during the treatment period and for at least 30 days after the last dose of study treatment.

The investigator is responsible for ensuring that male and female study participants understand how to correctly use the methods of contraception described in Appendix 1

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 2 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, neuromuscular, psychiatric, auto-immune or neurological disorders .
2. History of convulsions.
3. Any other condition that is capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data.
4. History of any malignancies or chemotherapy/radiation within the past 5 years excluding treated squamous carcinoma of the skin and adequately excised basal cell carcinoma
5. History of kidney, heart or lung transplants.
6. History or presence of rheumatoid arthritis.
7. Presence of hypokalaemia where the serum potassium is < lower limit of normal (LLN).
8. Presence of hypomagnesaemia where the serum magnesium is < LLN.
9. Fasting blood glucose ≥7mmol/L.
10. Serum glucose-6-phosphate dehydrogenase < LLN.
11. Abnormal renal function, as determined by creatinine clearance and considered as clinically significant by the investigator will be excluded.
12. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)

13. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
14. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
15. Excessive alkalinity of the urine (pH ≥9), as determined on Day -1.
16. Abnormal blood pressure (BP) as determined by the investigator.
17. QT interval corrected for heart rate according to Bazett's formula (QTcB) >450 milliseconds (msec). Participants with a known risk of QT prolongation will be excluded.

NOTES:

- For purposes of data analysis, only QTcB, will be used.

Prior/Concomitant Therapy

18. Past or intended use of over-the-counter or prescription medication including herbal medications, within 14 days prior to dosing unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study. Specific medications listed in Section 7.7 may be allowed.

Prior/Concurrent Clinical Study Experience

19. Where participation in the study would result in loss of blood or blood products in excess of 500 mL within 90 days.
20. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
21. Current enrolment or past participation within the last 90 days before signing of consent in this or any other clinical study involving an investigational study treatment.

Diagnostic assessments

22. Presence of Hepatitis B surface antigen (HBsAg) at screening or a Positive Hepatitis C antibody test result at screening.

NOTE: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

23. Positive pre-study drug/alcohol screen
24. Positive human immunodeficiency virus (HIV) antibody test
25. Regular use of known drugs of abuse

Other Exclusions

26. Sensitivity to heparin or heparin-induced thrombocytopenia

27. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy including allergy to quinolones that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.
28. Regular alcohol consumption within 6 months prior to 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 (125 mL) of wine or 1 (25 mL) measure of spirits.
29. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening.

6.3. Lifestyle Restrictions

- Study participants must avoid direct exposure to sunlight and UV radiation for 24 hrs after dosing, due to potential for photo-toxicity reactions.
- Participants must not drive or operate machinery for 24 hours following the dose of study medication.

6.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to the first dose of study medication until after the final dose.
- Participants will be administered the treatment in the fasted state.
- Following an overnight fast of at least 10 hrs, participants should be administered the study drug with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hrs post-dose. Water is allowed as desired except for one hr before and after drug administration. Participants should receive standardized meals scheduled at the same time in each period of the study.
- Adequate hydration must be maintained, whilst taking into consideration the 1 hr water restriction pre-and post study medication dosing.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hrs before the start of dosing until after collection of the final PK sample.

- During each dosing session, participants will abstain from alcohol for 24 hrs before the start of dosing until after collection of the final PK sample.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hrs before the start of dosing until after collection of the final PK sample, at each dosing session. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Table 4 Study Treatments

	Study Treatment	
	Test Product	**Reference Product**
Study Treatment Name:	GR37547/Ciprofloxacin 500 mg (CIPVAL™)	Ciproxin
Dosage formulation:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	500 mg Ciprofloxacin	
Route of Administration	Route: Oral Duration: single dose	
Dosing instructions:	1 tablet to be taken orally with 240 mL water.	
Physical Description:	White to off white capsule shape with break line on upper side and embossed “GSK500” on lower side.	Nearly white to slightly yellowish film coated oblong tablets with break line and “CIP 500” marked on upper side and “BAYER” on lower side.
Manufacturer /Supplier	GlaxoSmithKline Pakistan Limited, F-268, Karachi 75700, Pakistan.	Bayer Pharma AG/Bayer plc, U.K.

7.2. Dose Modification

Not applicable.

7.3. Method of Treatment Assignment

Participants will be assigned to one of two sequences (A-B or B-A) in accordance with the randomisation schedule generated by PAREXEL Biostatistics, prior to the start of the study, using validated software. Randomization numbers will be assigned sequentially. Possible replacements will be handled according to Section 5.2.

A description of each regimen is provided in Table 5. Treatments administered are as follows:

- Treatment A – Test GR37547 Ciprofloxacin 500 mg tablets (CIPVAL™)
- Treatment B – Reference 500 mg Ciprofloxacin tablets (Ciproxin)

On Day -1, participants will be assigned a unique randomization number. The randomization number encodes the participant's assignment to one of the 2 sequences. On Day 1, each participant will be administered a single dose of open label study treatment. After a washout period of 7-14 days, each participant will be administered a single dose of the other treatment not previously received.

Table 5 Description of each treatment sequence

Sequence	Number of Participants Per Group	Treatment Period 1	Treatment Period 2
A-B	13	Treatment A (GR37547)	Treatment B Reference
B-A	13	Treatment B Reference	Treatment A (GR37547)

7.4. Blinding

This is an open label study; potential bias will be reduced by assigning treatment by randomization.

7.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- The final disposition of unused study treatment will be handled as per GSK's requirements after study conduct.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- 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.

7.6. Treatment Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When participants are dosed, 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 site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.7. Concomitant Therapy

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

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The ciprofloxacin SMPC [**CIPROXIN** Package Insert, 2016] should be consulted for detailed information regarding interaction with concomitant therapy.

Participants must abstain from taking prescription or non- prescription drugs (including vitamins and dietary or herbal supplements) for 14 days before the start of the study until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

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 investigator in consultation with the Medical Monitor if required. Please refer to the summary of interactions with other medicinal products in the Package Insert for Ciproxin.

7.8. Treatment after the End of the Study

This is a study in healthy participants who will not receive any treatment after the end of the study.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants will be permanently withdrawn from study treatment, at the discretion of the investigator in the event of the following medical reasons after receiving the first dose of study medication:

- anaphylaxis,
- sensitivity reactions (e.g. pharyngeal or facial oedema, dyspnoea, rash, severe dermatologic reactions,)
- tendinopathy and tendon rupture
- liver events (see Section 8.1.1).
- positive pregnancy test
- vomiting within 4 hours (approximately 2 × the median t_{max}) of the reference product
- other AEs related to study treatment at the investigator discretion

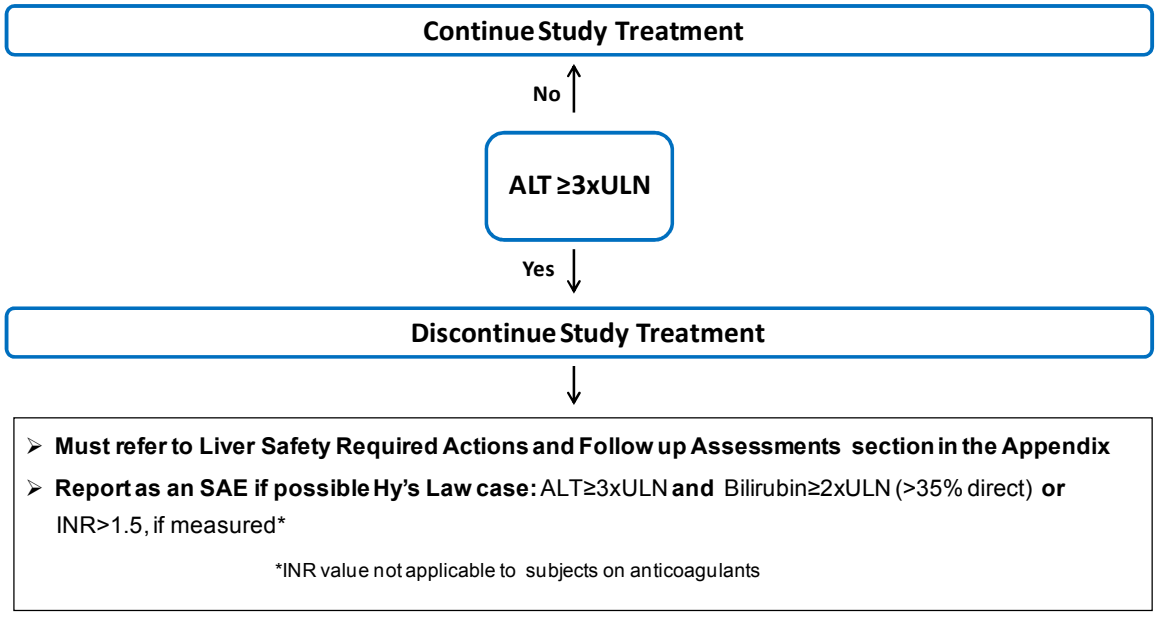
8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm in Figure 2, or if the investigator believes that it is in the best interest of the participant.

Study treatment will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Figure 2 Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3.

8.1.2. QTc Stopping Criteria

The *same* QT correction formula must be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all* QT corrected *(QTc) data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

The QTcB should be based on single QTcB values of ECGs obtained over a brief recording period.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

A participant that meets either of the bulleted criteria below will be withdrawn from study treatment.

- QTc, QTcB, >500 msec,

- Change from baseline: QTc >60 msec

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Temporary Discontinuation

Participants withdrawn from study treatment, will continue in the study until completion of the follow up visit for the study period.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up. Additional assessments may be performed at the discretion of the investigator.

8.3. Lost to Follow Up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. During screening the following will be completed:
    - Demographic parameters will be captured: Year of birth, sex, race and ethnicity.
    - Medical /Medication /family history will be assessed as related to the inclusion/exclusion criteria in Section 6.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Blood samples will be collected as per SoA.
    - The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
    - Samples will be destroyed within 6 months after the clinical execution of the study has been completed.

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment /study (see Section 8).

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

- All SAEs will be collected from the time a participant consents to participate in the study until the follow-up visit at the time points specified in the SoA (Section 2).
- AEs will be collected from the start of IP administration and until the follow-up contact at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hrs, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hrs of it being available.
- 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 participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non serious AEs of special interest (as defined in Section 3.3.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific

regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected from the start of study treatment until 5 days after the last dose or until the follow up visit where indicated.
- If a pregnancy is reported, the investigator should inform GSK within 24 hrs of learning of the pregnancy and should follow the procedures outlined in Appendix 1.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be a SAE.

9.3. Treatment of Overdose

For this study, any dose of study treatment GR37547 or comparator greater than 500 mg ciprofloxacin within a 24-hr time period will be considered an overdose. Symptomatic and supportive treatment is recommended.

In the event of acute excessive oral over dosage, routine emergency measures must be followed. In addition, ECG, renal function and urine pH should be monitored. Administer magnesium or calcium containing antacids which reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic ciprofloxacin exposure. The principal investigator will be responsible for the appropriate medical management of any participant who has an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until ciprofloxacin can no longer be detected systemically (at least 3 days).
3. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2). 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.

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Temperature, pulse rate, respiratory rate, and BP will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs will be measured in a supine position after 5 minutes rest and will include temperature, systolic and diastolic BP, respiratory rate and pulse. Three readings of BP and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF.
- Participants will not be dosed if their average pre-dose SBP on Day 1 is <95 mm Hg or their average resting ventricular rate is ≤45 beats per minute.
- Pre-dose vital signs will be collected at -2.00 to 0.00 hrs. Following completion of the pre-dose procedures the appropriate dose of study medication will be administered.

Vital signs post dose will be obtained within ± 30 min.

9.4.3. Electrocardiograms

Single 12-lead ECGs will be obtained at the Screening visit, Day 1 (to co-incide with t_{max}), and on Day 2 at the time of discharge, as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT,

and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

9.4.4. Clinical Safety Laboratory Assessments

- All clinical laboratory assessments will be performed by the local laboratory.
- Refer to Appendix 5 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory results , document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF or equivalent. Clinically significant abnormal laboratory findings are those which are not usually expected in a healthy volunteer.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 5, must be conducted in accordance with the PAREXEL laboratory manual, PAREXEL standard operating procedures (SOPs) and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF or equivalent.
- Refer to the PAREXEL SOPs for appropriate processing and handling of samples to avoid duplicate/ and or additional blood draws.

9.4.5. Suicidal Risk Monitoring

Ciprofloxacin is considered to be a CNS-active drug. There have been some reports of rare instances of psychiatric reactions such as depression and psychosis leading to suicidal ideation as reported in the product label [**CIPROXIN** Package Insert, 2016] in some patients being treated with ciprofloxacin for bacterial infections. This risk is expected to be lower with a single dose versus a course of treatment. Nevertheless, GSK considers it important to monitor for such events before and during clinical studies with compounds such as this.

Study participants receiving ciprofloxacin should be appropriately observed for suicidal ideation and behaviour or any other unusual changes in behaviour. Consideration should be given to discontinuing further dosing with the study medication in participants who experience signs of suicidal ideation or behaviour.

9.5. Pharmacokinetics

Pharmacokinetic sampling time-points are discussed in the SoA in Section 2.

- Whole blood samples of approximately 6 mL will be collected into lithium heparin tubes, for measurement of plasma concentrations of ciprofloxacin as specified in the SoA. A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples is provided in the PAREXEL Laboratory Manual. The actual date and time (24-hr clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of ciprofloxacin.
- Each plasma sample will be divided into 2 aliquots of not less than 1.2 mL plasma each (one for analysis and one backup).
- Samples collected for analyses of ciprofloxacin plasma concentration may also be used to evaluate safety related to concerns arising during or after the study.
- Pre-dose PK samples will be collected within 15 minutes prior to dose
- Post dose samples for 0.50-2.00 hrs will be collected within ±2 minutes ; samples for 2.50 – 8.00 hrs will be collected within ±5 min; and samples for 12.00 – 24.00 hrs will be collected within ± 10 min.
- Samples collected outside these recommended time windows will be recorded as protocol deviations
- Participant confidentiality will be maintained. At visits during which whole blood samples are also taken for laboratory or other tests, one sample of sufficient volume can be used.
- A validated bioanalytical method, as described in the PAREXEL bioanalytical protocol will be used for quantitative analysis.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

Refer to Analysis Plan (Appendix 6).

Bioequivalence

The primary objective of this study is to demonstrate BE between the test 500 mg tablet formulation GR37547 and the reference formulation, based on PK endpoints C_{max} and $AUC_{(0-t)}$ of ciprofloxacin.

The null hypothesis is that the true ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, $\mu_{(Test)}/\mu_{(Reference)}$, for the C_{max}, or $AUC_{(0-t)}$, is either <0.80 or >1.25 for plasma ciprofloxacin.

The alternate hypothesis is that the true ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment for both the C_{max}, and $AUC_{(0-t)}$, is ≥ 0.80 and ≤ 1.25 for plasma ciprofloxacin.

Symbolically this is expressed as follows:

H0: $\mu_{(Test)}/\mu_{(Reference)} < 0.80$ or $\mu_{(Test)}/\mu_{(Reference)} > 1.25$

i.e., treatments are not bioequivalent.

versus

Ha: $0.80 \leq \mu(Test)/\mu(Reference) \leq 1.25$

i.e., treatments are bioequivalent.

For each PK parameter designated as a primary endpoint, a two one-sided t-test (TOST)[Schuirmann, 1987] procedure with $\alpha=0.05$ for each one-sided test will be used to test this set of hypotheses. Bioequivalence will be declared if the 90% CI for the true ratio of test to reference geometric means falls entirely within the range of 0.80 to 1.25 for all primary parameters.

For BE to be declared, the null hypothesis must be rejected, for all primary parameters C_{max}, and $AUC_{(0-t)}$, for ciprofloxacin.

10.1. Sample Size Determination

Sample Size Rationale:

Bioequivalence is to be determined on the basis of the endpoints C_{max} and $AUC_{(0-t)}$ of ciprofloxacin.

Intra participant coefficient of variation (CV_w) estimates in recent published data for ciprofloxacin were in the range of 12 to 18% for the primary endpoints of ciprofloxacin [Hassan , 2007; Cuadrado, 2004] which are in line with older published data [Galicia , 1998] . For the oral formulation, AUC data (CV_w approximately 11-12%) generally were less variable than C_{max} data (15-18%) and thus the latter should be considered for sample size calculation.

Hence, the sample size for this trial was determined based on maximum observed intra participant CV of 18%.

Based on a BE range of 80.00% to 125.00% for C_{max} and $AUC_{(0-t)}$, for ciprofloxacin assuming intra participant CV to be 18% and a "test/reference" mean ratio of 0.95; 22 evaluable subjects are needed to achieve a power of 90% at an alpha level of 0.05 for the single test for testing BE.

Approximately 26 eligible participants (approximately 19% in excess of number needed to complete) will be entered into the study to complete the study with at least 22 evaluable participants. See Section 5.2

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 6 Description of Populations for Analysis

Population	Description
Enrolled	All participants who sign the ICF
Randomized	All participants assigned to study treatment
Safety	All randomized participants who received at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK	All subjects who complete the study and for whom primary PK parameters can be calculated for all treatment periods will be included in the statistical PK analysis of the study.

10.3. Statistical Analyses

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the statistical methodology, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in the clinical study report.

See Appendix 6 for a list of Tables, Figures and Listings to be appended in the clinical study report.

10.3.1. PK Analyses

Pharmacokinetic analysis will be the responsibility of the PAREXEL Quantitative Clinical Development (QCD) department. Plasma ciprofloxacin concentration-time data will be analysed by non-compartmental methods with Phoenix WinNonlin 6.3. The PK parameters will be calculated for each participant and treatment using non-compartmental analysis and using the actual sampling time intervals (relative to IMP administration) recorded during the study.

From the plasma concentration-time data, the following PK parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to C_{max} (t_{max}), area under the plasma concentration-time curve [AUC(0-∞) and $AUC_{(0-t)}$], and apparent $t_{1/2}$ of ciprofloxacin.

Participants who experience emesis during the course of the study will be deleted from the statistical analysis if vomiting occurred within 4 hrs which is approximately twice the median t_{max} [**CIPROXIN** Package Insert, 2016]. For participants with pre-dose plasma concentrations, their data may be included without any adjustments in all PK measurements and calculations if the pre-dose concentration is ≤ 5% of C_{max}. If the pre-dose value is > 5% of C_{max}, the participant's data may be dropped from all BE evaluations.

The available concentration data of the participants excluded due to vomiting, and of those who did not complete the PK sampling will only be listed; it will not be presented in descriptive statistics or included in PK evaluations or formal statistical analysis.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All PK data will be archived by the study sponsor GSK.

Statistical analyses of the PK parameter data will be the responsibility of PAREXEL Biostatistics.

10.3.2. Protocol Deviations and Changes to Planned Analyses

Permission from the sponsor in writing will be obtained should any changes be required to the clinical study protocol. Should the safety of the subjects necessitate immediate action, which represents a deviation from the clinical study protocol, the sponsor will be informed as soon as possible.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan .

Protocol deviations and changes to planned analyses will be described in the clinical study report.

10.3.3. PK Parameters

Calculation of the PK parameters will be made with Phoenix WinNonlin 6.3 (Certara, L.P., 1699 South Hanley Road, St Louis, Missouri 63144, USA). The PK parameters will be calculated for each subject and treatment using non compartmental analysis and using the actual sampling time intervals (relative to IMP administration).

10.3.3.1. Primary Pharmacokinetic Parameters for ciprofloxacin

- Maximum observed plasma concentration (C_{max})
- Area under the plasma concentration versus time curve, from time zero to t, where t is the time of the last quantifiable concentration ($AUC_{(0-t)}$).

10.3.3.2. Secondary Pharmacokinetic Parameters for ciprofloxacin

- Time to maximum observed plasma concentration (t_{max})
- Area under the plasma concentration versus time curve, with extrapolation to infinity ($AUC_{(0-\infty)}$)
- Apparent terminal elimination half-life ($t_{½}$)
- Percent area under the curve extrapolated ($\%AUC_{ex}$).

10.3.4. Analysis of Bioequivalence

Table 7 Statistical Analysis Methods to be used for Endpoints

Endpoint	Statistical Analysis Methods
Primary	Following log-transformation of derived pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$ of ciprofloxacin will be analysed by using analysis of variance with sequence, subject (sequence), treatment and period effects. Point estimates for the adjusted means on the loge scale, the mean difference between treatments and associated 90% CIs for the difference Treatment A - Treatment B will be constructed using the residual variance. These point estimates and confidence intervals will then be exponentially back-transformed to obtain adjusted (least square) geometric means for each treatment and point estimates and associated 90% confidence intervals for the ratio, Treatment A/Treatment B. Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If the assumptions are

Endpoint	Statistical Analysis Methods
	seriously violated then alternative statistical methods will be considered.
Secondary	$AUC_{(0-\infty)}$ of ciprofloxacin will be analysed as per primary analysis; t_{max} of ciprofloxacin will be analysed using a nonparametric test to compute point estimate of the median and associated 90% confidence intervals for the median differences, Treatment A –Treatment B %AUCex will not be statistically analysed. A summary will be created. For t½ the n, median, minimum, and maximum values will be presented

10.3.5. Safety Analyses

All safety analyses will be performed on the Safety Population.

Safety variables will include vital signs and clinical chemistry results. Adverse events and concomitant medication will also be listed and summarized by treatment.

10.3.6. Other Analyses

No other analyses are planned.

10.3.7. Interim Analyses

No interim analysis is planned.

11. REFERENCES

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CIPRO (Ciprofloxacin hydrochloride tablets, Ciprofloxacin Oral Suspension, Summary of Product Characteristics) Product Information. November, 2011. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019537s074,020780s032lbl.pdf)

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12. APPENDICES

12.1. Appendix 1: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

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

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 8 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for 5 days after each dose of study treatment.
- Refrain from donating sperm for duration of study and for 5 days after the last dose of study treatment

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8.

Table 8 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and*

the preferred and usual lifestyle of the participant.)

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing should be performed on Day -1 during the treatment period.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 10 mIU/mL (dipstick) and serum 0.100 to 10 000 mIU/mL (automated) will be performed and assayed in a certified laboratory.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- 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 termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will

be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. 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 participant who becomes pregnant while participating

- will discontinue study treatment or be withdrawn from the study

12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

Financial disclosure will not be collected for this study, as data will not be used to support any marketing applications with any regulatory authorities

Informed Consent Process

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

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant 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 participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

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 a GSK site or other mutually agreeable location.

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

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

Study information and tabular study results, from this protocol will be posted on the US National Institutes of Health's website www.ClinTrials.gov, other publically-accessible sites, and the GSK Clinical Trials Register. In addition, results may also be published in peer-reviewed publications, to ensure the scientific integrity and credibility of publication activities performed by or on behalf of the company. Access to analyzable datasets from clinical studies will be granted through a secure system, following an independent assessment of the scientific merit of a rigorously defined research question from a third party.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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 ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary 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.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the PAREXEL SOPs .
    - SOP-EP.CL-WW-009-01: Data Collection, Transcription, Quality Control and Clarification
    - MAN-EP.CL-WW-044-01: Data Collection, First Time Quality and Correction of Data Entries

Study and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.3. Appendix 3: Liver Safety: Required Actions and Follow-up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 3 days of last dose
• Serum creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies,</td></tr>
</table>

Liver Chemistry Stopping Criteria	
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • 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 high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: 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

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA,et.al.. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding deemed clinically significant by the investigator), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (egg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF or equivalent.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant 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 CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Paper CRF
• The primary mechanism for the Investigator to report SAEs and updated data on previously reported SAEs to GSK, will be the SAE paper data collection tool (form). • Facsimile transmission of the GSK SAE reporting form (paper) is the preferred method to transmit this information from the Investigator site to the **LOC Pharmacovigilance team /medical monitor .** • The LOC Pharmacovigilance team will enter the SAE into the Local Affiliate Module (LAM) with the SAE copy attached. The SAE will then be visible to Central Pharmacovigilance. • The Pharmocovigilance assistant will report the SAE to the Regulatory Authority (MCC) • 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 or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • The Investigator must ensure that SAEs are reported to the local ethics committee, within the required timelines. • **Contact for SAE reporting:** **GSK, South Africa - Pharmacovigilence** **Facsimile:** PPD

12.5. Appendix 5: Clinical Laboratory Tests

- The tests detailed in Table 1will be performed by the local laboratory.
- If the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [fasting]	Calcium	Alkaline phosphatase	glucose -6-phosphate dehydrogenase (G6PD)
	Chloride	Magnesium	Lactate dehydrogenase (LD)	
Coagulation Profile	• PT and aPTT			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Breath alcohol and urine drug screen (to include at minimum: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine (phenylcyclohexalpiperidine), tetrahydrocannabinol, methadone, methamphetamine, tricyclic antidepressants, oxycodone			

Laboratory Assessments	Parameters
	and propoxyphene) • Cotinine • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] Hepatitis C RNA test for Hepatitis C antibody positive Participants The results of each test must be entered into the CRF or equivalent.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 3. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

12.6. Appendix 6: Analysis Plan

Rules for handling decimals

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of safety data:

All data will be listed according to the number of decimal places presented in the source data.

Mean and median will be tabulated to one more decimal place than the source data. Minimum and maximum values will be tabulated to the same number of decimal places as the source data.

Standard deviation (SD) will be tabulated to two more decimal places than the source data.

A maximum of three decimal places will apply to all summary statistics.

Missing data

AEs with missing start dates/times will be handled as follows for the tabulations:

- Missing start date:
    - If the start date is completely missing but the end date is known and shows that the AE ended on or after the dosing date in a specific treatment period, then the start date will be imputed as the day of dosing in that period (therefore first dosing in the run-in period).
    - If the end date is known and shows that the AE ended before the first dosing date in the run-in period, then the screening date will be used for the start date.
    - If the end date is known and shows that the AE ended before the dosing date in the treatment period (but after dosing in the run-in period), then the first dosing date of the run-in period will be used for the start date.
    - If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the date of first dosing in the run-in period will be used.
- Missing start day:
    - If only the start day is missing the day will be imputed as the first day on which a dose was given in that month unless the end date is known and shows that the AE ended before a dose was given in that month; in which case the date will be imputed as 01.

  - If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known month. If the month is not a dosing month the date will be imputed as 01.

- Missing start day and month:

  - If the start day and month are missing the date will be imputed as the first day of dosing in the known year unless the end date is known and shows that the AE ended before a dose was given in that year; in which case the start day and month will be imputed as 01Jan or with the date of screening if this is later. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known year. If the year is not a year of dosing then the date will be imputed as 01Jan or with the date of screening if this is later.

- Missing times

  - Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

Presentation of PK Data, Descriptive Statistics and PK Assessment

This section describes outputs to be presented.

The actual blood sampling times and time deviations will be listed for each participant dosed, treatment and scheduled sampling time. A listing of plasma concentrations of ciprofloxacin treatment will be provided.

Summary table reflecting summary statistics (n, arithmetic mean, geometric mean, median, coefficient of variation, standard deviation, minimum and maximum) per treatment will be provided for plasma concentrations of ciprofloxacin

Concentrations below the lower limit of quantification (LLOQ) will be indicated as below the limit of quantification (BLQ). These BLQ concentrations will be handled as follows:

- For descriptive statistics, pre-dose BLQ concentrations will be substituted by zeros. All other BLQ values will be substituted by ½LLOQ value before the calculation of the summary statistics. Values reported as 'NS' (no sample) will be set to "missing".

- For PK assessment, all BLQ values at pre-dose and in the absorption phase, before the first reported concentration, will be substituted by zeros. The BLQ values between evaluable concentrations will be substituted by ½LLOQ, before the calculation of the PK parameters. The terminal BLQ values will be set to missing. These measures are taken to prevent an over-estimation of AUC.

- For PK calculations, missing concentrations will be deleted, resulting in an interpolation between the nearest two concentration values.

A listing for PK parameters of ciprofloxacin per treatment will be provided. A summary table reflecting summary statistics (n, arithmetic mean, geometric mean, median, coefficient of variation, standard deviation, minimum and maximum) per treatment will be provided for PK parameters of ciprofloxacin.

The individual plasma ciprofloxacin concentration versus actual time profiles for each participant and treatment, as well as the mean (arithmetic and geometric) plasma ciprofloxacin concentration versus scheduled time profiles for each treatment, will be presented graphically on a linear-linear and log-linear scale. Individual plasma concentrations will be presented using actual, rather than planned, sampling times. Combined individual concentration versus time graphs per treatment will also be presented on a linear-linear scale, together with the geometric mean values. The adjusted geometric mean ratio with 90% CI will be presented graphically . The individual log-linear graphs reflecting the WinNonlin modelling results, will be presented using SAS.

The data listings, descriptive statistics, statistical analysis and graphs of this study will be generated using SAS/STAT and SAS/GRAPH software[1].

Data Precision

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings concentration data.

The individual plasma concentration will be reported to the same precision as the source data (e.g., if the source data is presented to five significant digits, the individual values will be presented to five significant digits).

The mean, SD, geometric mean and median will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits.

Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.

Geometric coefficient of variation (CV) % will be presented to once decimal place.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of PK parameters.

Individual PK parameters will be presented to four significant digits, with the exception of t_{max}, which will be presented to two decimal places. In addition, PK parameters

[1] SAS Version 9.2 or higher of the SAS System. Copyright© 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, North Carolina, USA.

directly derived from source data (e.g., $C_{max)}$ will be reported with the same precision as the source data (if this is not four significant digits).

The mean, geometric mean, median and SD values will be reported to four significant digits, all other descriptive statistics will be reported to three significant digits except for CV% which will be presented to one decimal place. For t_{max} the minimum and maximum will be presented to two decimal places and the rest of the descriptive statistics to three decimal places.

Estimates and confidence intervals in the form of percentages will be presented two decimal places.

Source data will be used in all derived PK parameter calculations without prior rounding.

Analysis of Bioequivalence

Refer to Table 6.

The following SAS code will be used, with the treatments sorted in the order reference first and then test:

ODS OUTPUT LSMeans=lsmean estimates=est nobs=nobs Overall ANOVA=anova;

PROC GLM DATA=pk ALPHA=0.1;

BY Analyte Parameter;

CLASS treatment period participant sequence[2]

MODEL var= treatment period sequence participant (sequence)/ clparm;

(where var = log [Cmax], log[AUC(0-t)])

OUTPUT OUT= routput R=res P=pred;

LSMEANS treatment / pdiff=control('A') CL;

ESTIMATE 'Test versus Reference' treatment 1 -1;

RUN;

[2]SAS Version 9.2 or higher of the SAS System. Copyright© 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, North Carolina, USA.

Bioequivalence of the test and reference products will be assessed on the basis of the 90% confidence intervals for estimates of the geometric mean ratios between the primary PK parameters of the test and reference products in relation to the conventional bioequivalence range of 80.00% to 125.00%.

Presentation of Baseline Characteristics and Safety Data

Baseline characteristics and safety data will be presented as mentioned below. Data captured but not presented as listed or summarized data will be available in the CRFs or the source data capture system.

Demographic and anthropometric data will be listed for all participants in the safety population. Demographic characteristics will be tabulated by treatment (n, mean, median, standard deviation, minimum and maximum for age and BMI; and frequency counts and percentages for race, age groups and sex).

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and listed and summarized by treatment for all participants in the safety population.

Vital signs data will be listed and summarized for all participants in the safety population.

List of Tables, Figures and Listings

The following tables, figures and listings will be provided for inclusion into the mentioned sections of the clinical study report.

Tables

Demographic characteristics

Statistical analyses of ciprofloxacin PK parameters (ANOVA)

Non Parametric Analysis of ciprofloxacin PK parameter

Plasma ciprofloxacin concentration (unit)

Plasma ciprofloxacin PK parameter (unit)

Adverse events summary by treatment

Concomitant Medication summary by treatment

Summary Statistics of Vital Signs Values

Summary Statistics of Chemistry Values.

Summary Statistics of Haematology Values.

Figures

Plasma ciprofloxacin arithmetic and geometric mean concentrations (unit)

Median concentration vs. Time for ciprofloxacin

Combined individual plasma ciprofloxacin concentrations (unit)

Individual plasma ciprofloxacin concentrations (unit) (linear-linear scale and log-linear scale)

Adjusted geometric mean treatment ratio (with 90% CI) for ciprofloxacin

Listings

Statistical output

Participant disposition

Randomization

Demography and anthropometry

Adverse events

Concomitant Medication

Vitals Signs

Haematology

Chemistry

Urinalysis

12-ECG Lead

Actual blood sampling times

Plasma ciprofloxacin concentrations (unit)

Plasma ciprofloxacin PK parameters (unit)

The bulleted lists above indicate requirements and are not necessarily the exact names of each table, figure or listing. The naming conventions as provided will be adhered to as far as feasible, but if deemed necessary the name of the output might be changed to fit the data.

12.7. Appendix 7: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
APTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
$AUC_{(0-\infty)}$	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
$\%AUC_{ex}$	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 participant across all treatments
BE	Bioequivalence
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CV	Coefficient of variation
C_{max}	Maximum observed concentration
CPK	Creatine phosphokinase
CRF	Case Report Form
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HRT	Hormone replacement therapy
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International Normalized Ratio
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IP	Investigational Product
IRB	Institutional Review Board
kg	Kilogram
LAM	Local Affiliate Module
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal

MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
Msec	Milliseconds
PK	Pharmacokinetic
PT	Prothrombin Time
QTc	QT corrected
QTcB	QT interval corrected for heart rate according to Bazett's formula
RBC	Red blood cells
SAE	Serious adverse event(s)
SBP	Systolic Blood Pressure
SD	Standard deviation
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
t½	Terminal phase half-life
Tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
WBC	White blood cells
WCBP	Women of Childbearing Potential

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