

## TITLE PAGE

**Protocol Title:** An open-label, randomised, single-dose, two-period cross-over study to evaluate bioequivalence of GSK3542503 hydrochlorothiazide + amiloride hydrochloride 50mg: 5mg fixed dose combination tablets versus reference product in healthy adult participants under fasting conditions

**Protocol Amendment Number:** 01

**Short Title:** Bioequivalence study between GSK3542503 hydrochlorothiazide + amiloride hydrochloride 50 mg: 5 mg tablets and reference product in healthy adult participants under fasting conditions.

**Compound Number:** GSK3542503

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**PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE**

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2016N288797_01	12-JAN-2017
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**Amendment 01 [12-JAN-2017]**

**Overall Rationale for the Amendment:** This protocol amendment is to correct the asset number for the hydrochlorothiazide and amiloride hydrochloride fixed dose combination. The asset number in the original protocol, GR77494 is amiloride. The asset number for the fixed dose combination of hydrochlorothiazide and amiloride hydrochloride, is GSK3542503. All references to asset GR77494 have been replaced with GSK3542503 throughout the protocol. There are no other changes.

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## 1. SYNOPSIS

**Protocol Title:** An open-label, randomised, single-dose, two-period cross-over study to evaluate bioequivalence of GSK3542503 hydrochlorothiazide + amiloride hydrochloride 50 mg: 5 mg fixed dose combination tablets versus reference product in healthy adult participants under fasting conditions.

**Short Title:** Bioequivalence study between GSK3542503 hydrochlorothiazide + amiloride hydrochloride 50 mg: 5 mg tablets and reference product in healthy adult participants under fasting conditions.

### Rationale:

This study will determine if GSK3542503 (marketed as BIDURET<sup>TM</sup>), manufactured by Panacea Biotec Ltd, India is bioequivalent to reference product, Moduretic, manufactured by Merck Sharpe and Dome Limited, United Kingdom (UK). Both products are combination diuretics of hydrochlorothiazide and amiloride hydrochloride, 50 milligrams (mg): 5 mg.

### Objectives and Endpoints:

Objectives	Endpoints
<b>Primary</b> <ul style="list-style-type: none"> <li>To determine if 50 mg HCTZ/5 mg amiloride hydrochloride (GSK3542503) tablets are bioequivalent to reference 50 mg HCTZ/5 mg amiloride hydrochloride tablets in healthy adult participants under fasting conditions.</li> </ul>	<ul style="list-style-type: none"> <li>Plasma PK parameters: <math>AUC_{(0-t)}</math> and <math>C_{max}</math>, for hydrochlorothiazide and amiloride in relevant treatments.</li> </ul>
<b>Secondary</b> <ul style="list-style-type: none"> <li>To measure secondary PK parameters of 50 mg HCTZ/5 mg amiloride hydrochloride tablets (GSK3542503) relative to reference 50 mg HCTZ/5 mg amiloride hydrochloride in healthy adult participants under fasting conditions.</li> <li>To compare the safety and tolerability of GSK3542503 with reference product 50 mg HCTZ/5 mg amiloride hydrochloride, , in healthy adult participants under fasting conditions.</li> </ul>	<ul style="list-style-type: none"> <li>Plasma PK parameters: <math>AUC_{(0-\infty)}</math>, <math>t_{max}</math>, <math>\%AUC_{ex}</math> and <math>t_{1/2}</math> for hydrochlorothiazide and amiloride in relevant treatments.</li> <li>Adverse events (AE), clinical laboratory values (Biochemistry) and vital signs</li> </ul>

$AUC_{(0-\infty)}$  = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; % $AUC_{ex}$ = Percentage of  $AUC_{(0-\infty)}$  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;  $C_{max}$ = Maximum observed concentration; HCTZ= Hydrochlorothiazide; Pk= Pharmacokinetic;  $t_{1/2}$ = Terminal phase half-life;  $T_{max}$ = Time of occurrence of  $C_{max}$

### **Overall Design:**

This is a Phase I, open label, balanced, randomised, single dose, two-way crossover study, enrolling 42 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:**

A maximum of 42 participants will be randomized to yield at least 32 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:** GSK3542503 (BIDURET<sup>TM</sup>), a hydrochlorothiazide 50 mg and amiloride hydrochloride 5 mg fixed dose combination.
- **Treatment B - Reference:** Moduretic, a hydrochlorothiazide 50 mg and amiloride hydrochloride 5 mg fixed dose combination.

### 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 7 days post last dose or at discontinuation)	Notes
		Day -1	Day 1	Day 2	Day 3		
Informed consent	X						
Inclusion and exclusion criteria	X	X					Refer to Section 6. Recheck clinical status before randomization and/or 1st dose of study medication.
Admission to the Unit (domiciled)		X	X	X			Participants to be admitted on Day -1 of each treatment period, and discharged after the 24 hour PK sample, on Day 2.
Outpatient Visits	X				X		At the end of treatment period 2, participants will have a brief medical exam, vital signs (VS) and lab assessments taken at 48 hours post dose .
Discharge				X			Participants will be discharged from the unit following the collection of the 24 hour PK samples and following review by a doctor to assess participant safety. Participants who have normal safety assessment results on discharge do not require a follow up.
Phone Call						X	If a participant's safety assessments (medical exam, VS, Lab assessments) are abnormal and clinically significant at Treatment Period 2 discharge, then a follow up phone call is required within 7 days. An outpatient clinic visit may be required. Enquiries on the participant's general health, including any AEs/SAEs/concomitant medication should be recorded in the medical notes.

Procedure	Screening (Day -21 to Day -1)	Treatment Periods 1 and 2				Follow-up (within 7 days post last dose or at discontinuation)	Notes
		Day -1	Day 1	Day 2	Day 3		
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) can be performed at Day -1
Past and current medical conditions	X	X					
Pregnancy test (WOCBP only)	X	X					Serum β-hCG at screening. At Day-1, urine β-hCG
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. 1.
Laboratory assessments (include liver chemistries)	X	X			X		<b>Screening:</b> Participants are required to fast at least 10 hours prior to the Screening Laboratory assessment. Haematology, Biochemistry, Coagulation profile (PT and aPTT)and Urinalysis are assessed. <b>Day -1:</b> Haematology, Biochemistry and Urinalysis are assessed. <b>Day 3:</b> Biochemistry is assessed 48 hours post dose. Additional safety labs must be collected as deemed necessary at the Investigator's discretion.
Urine Drug/Urine Cotinine/Breath alcohol	X	X					

Procedure	Screening (Day -21 to Day -1)	Treatment Periods 1 and 2				Follow-up (within 7 days post last dose or at discontinuation)	Notes
		Day -1	Day 1	Day 2	Day 3		
12-lead ECG	X						
Vital signs	X	X	X	X	X		Vitals will be taken at screening, Day -1, pre-dose (Day 1) and at , 1.00, 2.00, 4.00, 6.00, 8.00 ,24.00 and 48 hours post-dose. Post dose vitals to be taken $\pm$ 30min of each timepoint.
Randomization		X					Day -1 of treatment period 1 only.
Study treatment			X				Day -1 results must be reviewed by physician prior to randomisation and dosing. Participants to be fasted 10.00hours 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			$\leftarrow$ ===== $\rightarrow$				Collected from the start dosing 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		$\leftarrow$ ===== $\rightarrow$					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.
Concomitant medication review		X	$\leftarrow$ ===== $\rightarrow$				

Procedure	Screening (Day -21 to Day -1)	Treatment Periods 1 and 2				Follow-up (within 7 days post last dose or at discontinuation)	Notes
		Day -1	Day 1	Day 2	Day 3		
Pharmacokinetics			X	X	X		<b>Day 1:</b> Pre-dose, 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, <b>Day 2:</b> 24.0 and 36.0 hours post dose <b>Day 3:</b> 48.0 hours post dose,  Pre-dose sample will be taken within 15 minutes before dose. Post dose samples for 0.33 -24 hours will be taken $\pm$ 2 min. Post dose samples for 36 and 48 hours will be taken $\pm$ 2 hours

- 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, GSK3542503 (containing hydrochlorothiazide 50 milligrams (mg) and amiloride hydrochloride 5 mg) tablets are marketed in India as BIDURET<sup>TM</sup>. This study is required to determine whether the test product GSK3542503/BIDURET<sup>TM</sup> is bioequivalent to the reference hydrochlorothiazide 50 mg/amiloride hydrochlorothiazide 5 mg 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

The cardiovascular disease hypertension is defined as the elevation of systolic and /or diastolic blood pressures (BP) to 140/90 mm Hg. Although asymptomatic, “benign” hypertension is a major risk factor for stroke, congestive heart failure and coronary artery disease. Thiazide diuretics and related phthalimidine derivatives have become the mainstay of antihypertensive regimens owing to their antihypertensive effects when used alone and their ability to enhance the efficacy of virtually all other antihypertensive drugs when used in combination [Gerber JG, 1990].

The combination of the diuretics Amiloride hydrochloride and hydrochlorothiazide (GSK3542503), are indicated for the treatment of hypertension, congestive heart failure and hepatic cirrhosis with ascites and oedema [MODURETIC Package Insert, 2015].

#### Amiloride Hydrochloride

Amiloride hydrochlorothiazide is a potassium-conserving (antikaliuretic) drug with mild (compared to thiazide diuretics) natriuretic, diuretic and antihypertensive activity. [Weiner IM, 1990].

These activities may be additive to the effects of thiazides or other saluretic-diuretic agents. The principle use of amiloride hydrochloride is to conserve potassium in selected patients receiving kaliuretic diuretic agents. The drug acts directly on the distal portion of the nephron inhibiting the reabsorption of sodium [Willem H. Birkenhager, 1990]. Amiloride hydrochloride usually begins to act within 2 hrs after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hrs and lasts about 24 hrs. Peak plasma levels are obtained in 3 to 4 hrs and the plasma half life varies from 6 to 9 hrs [APO-AMILIZIDE Package Insert, 2013]. Amiloride hydrochloride does not undergo metabolic transformation, and is not bound to serum proteins [DG Vida, 1981].

#### Hydrochlorothiazide (HCTZ)

Hydrochlorothiazide (HCTZ) is a diuretic and antihypertensive agent. It affects the renal tubular mechanism of electrolyte re-absorption [APO-AMILIZIDE Package Insert, 2013]. The exact mechanism of the antihypertensive effect of thiazides is unknown. HCTZ does not usually affect normal BP.

The PK properties of hydrochlorothiazide show that 70% of an oral dose is absorbed and it is excreted unchanged in the urine. It has a plasma half life of 5.6 to 14.8 hrs [MODURETIC Package Insert, 2015]. Time of occurrence of  $C_{max}$  ( $T_{max}$ ) is reached at 2.1 hrs, and maximum observed concentration ( $C_{max}$ ) is 280 ng/ milliliter (mL) after a 50 mg dose [Welling, 1986]. Hydrochlorothiazide is bound to plasma proteins to about 40% and accumulates in erythrocytes. The absorption in patients with hypertension is similar to healthy individuals, but decreased in patients with heart failure [Beermann, 1984].

### **Hydrochlorothiazide and amiloride combination**

The combination of HCTZ/ amiloride provides diuretic and antihypertensive activity (principally due to the HCTZ component) while acting through the amiloride component to prevent excessive potassium loss that may occur in patients receiving a thiazide diuretic. The onset of action of the combination is within 1 to 2 hrs and this action appears to be sustained for approximately 24 hrs [APO-AMILIZIDE Package Insert, 2013].

The optimal dosage should be established by the individual titration of the components. For hypertension the usual maintenance dose is 1 or 2 tablets of HCTZ 50 mg/amiloride 5 mg given once a day in divided doses. The dosage should not exceed 4 tablets a day [APO-AMILIZIDE Package Insert, 2013].

A detailed description of the chemistry, pharmacology, efficacy, and safety of Amiloride hydrochloride and hydrochlorothiazide is provided in the package insert for Moduretic.

### **3.3. Benefit/Risk Assessment**

Hydrochlorothiazide/ amiloride hydrochloride fixed dose combination was first approved in 1986 for the treatment of hypertension, congestive heart failure and hepatic cirrhosis with ascites and oedema, by the Medicines and Healthcare Product Regulatory Agency (MHRA), in the United Kingdom (UK).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of HCTZ/amiloride hydrochloride can be found in the Summary of Product Characteristics (SmPC) [MODURETIC Package Insert, 2015]. HCTZ/amiloride hydrochloride fixed dose combination has a well established safety profile.

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 this study are derived from the prescribing information from marketed formulations of HCTZ/amiloride hydrochloride tablets. Risks associated with chronic use or in patient types (e.g. patients with renal failure) 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
<b>Study treatment GSK3542503 and reference HCTZ/amiloride hydrochloride</b>		
Allergic reaction to the active substances or to any of the excipients	Contraindication : Urticaria or anaphylactic reactions may occur if a volunteer has hypersensitivity to HCTZ/amiloride or excipients.	Exclude participants with known hypersensitivity to HCTZ or amiloride hydrochloride or other sulphonamide derived drugs, or excipients including but not limited to lactose, guar gum and sunset yellow. .
Hyperkalaemia	Warning: Rapid increases in plasma potassium may lead to the development of acidosis.	Exclude participants taking potassium supplements. All study participants will undergo laboratory testing for renal function, in order to exclude patients with a creatinine clearance level below 30ml/min, and those with existing hyperkalaemia where the serum potassium level is > ULN. Study participants will be warned against consuming potassium rich foods and taking potassium supplements during participation the study. Laboratory tests will be used to monitor potassium levels, and creatinine level, during the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Electrolyte imbalance	Warning: Signs or symptoms of electrolyte imbalance could include dryness of the mouth, weakness, lethargy, drowsiness, restlessness, seizures, confusion, muscle pain or cramps, hypotension, oliguria, tachycardia, nausea or vomiting.	Study participants will undergo laboratory testing for sodium, chloride, potassium and magnesium for detection of electrolyte imbalance which may need to be treated. Patients will also be assessed for clinical signs of electrolyte imbalance through the collection of AEs during the study period.
Metabolic abnormalities	Warnings. Metabolic abnormalities such as gout, or diabetes may be precipitated.	A standard panel of chemistry laboratory assessments, will be performed prior to dosing and after each dose of study medication and reviewed for metabolic abnormalities.
Sensitivity reactions	Warning. Thiazides may activate or exacerbate Systemic lupus erythematosus .	Participants with a history of systemic lupus erythematosus will be excluded.
Ophthalmologic reactions	Warning: increased intra-ocular pressure, has been reported in patients using amiloride hydrochloride; and transient blurred vision and xanthopsia have been reported in patients taking HCTZ . Visual disturbances have been reported in patients taking the HCTZ/amiloride hydrochloride fixed dose combination.	Exclude participants with a history of sulphonamide or penicillin allergy which are risk factors for developing acute angle-closure glaucoma. Immediately discontinue study medication if participants present with any ocular complaints.
Hepatic disease	Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma	Exclude participants with active hepatic disease.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Study Procedures</b>		
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.
<b>Other</b>		
Not applicable	Not applicable	

### 3.3.2. Benefit Assessment

Participants enrolled into this study are healthy participants. There will be no direct benefits gained from participation in this study. The participants' involvement will be contributing to the PK analysis and safety profile of GSK3542503 compared to reference HCTZ/amiloride hydrochloride.

### 3.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants in this study, the potential risks identified in association with GSK3542503 tablets are justified by the anticipated benefits that may be afforded to patients for the treatment of hypertension congestive heart failure and hepatic cirrhosis with ascites and oedema.

## 4. OBJECTIVES AND ENDPOINTS

**Table 3 Study Objectives and Endpoints**

Objectives	Endpoints
<p><b>Primary</b></p> <p>To determine if 50 mg HCTZ/5 mg amiloride hydrochloride (GSK3542503) tablets are bioequivalent to reference 50 mg HCTZ/5 mg amiloride hydrochloride tablets in healthy adult participants under fasting conditions.</p>	<p>Plasma PK parameters: <math>AUC_{(0-t)}</math> and <math>C_{max}</math>, for hydrochlorothiazide and amiloride in relevant treatments.</p>
<p><b>Secondary</b></p> <p>To assess secondary PK parameters of 50 mg HCTZ/5 mg amiloride hydrochloride tablets (GSK3542503) relative to reference 50 mg HCTZ/5 mg amiloride hydrochloride in healthy adult participants under fasting conditions .</p> <p>To compare the safety and tolerability of GSK3542503 with reference product 50 mg HCTZ/5 mg amiloride hydrochloride, in healthy adult participants under fasting conditions.</p>	<ul style="list-style-type: none"> <li>Plasma PK parameters: <math>AUC_{(0-\infty)}</math>, <math>t_{max}</math>, <math>\%AUC_{ex}</math> and <math>t_{1/2}</math> for hydrochlorothiazide and amiloride in relevant treatments.</li> <li>Adverse events (AE), clinical laboratory values (Biochemistry) and vital signs</li> </ul>

AUC<sub>(0-∞)</sub> = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; %AUC<sub>ex</sub>= Percentage of AUC(0-∞) obtained by extrapolation; AUC<sub>(0-t)</sub>= Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments; t1/2= Terminal phase half-life

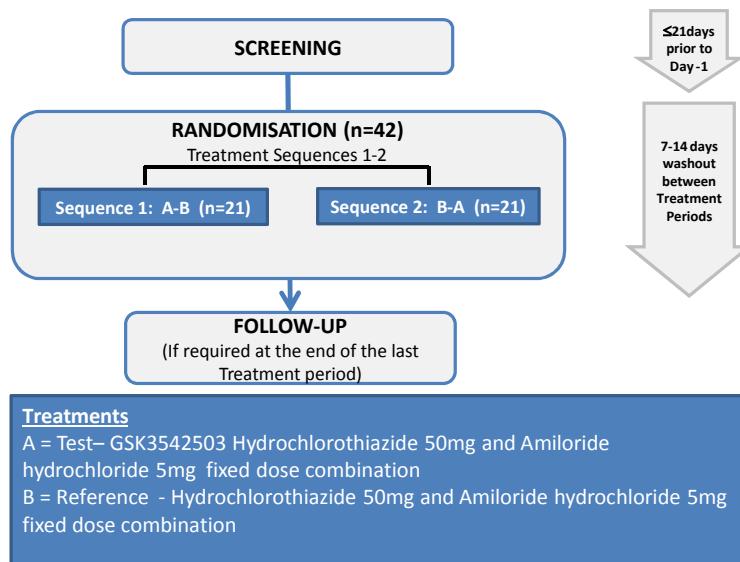
## 5. STUDY DESIGN

### 5.1. Overall Design

This is a Phase I, open label, balanced, randomised, single dose, two-way crossover study, enrolling approximately 42 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:** GSK3542503 (BIDURET<sup>TM</sup>), a hydrochlorothiazide 50mg and amiloride hydrochloride 5mg fixed dose combination.
- **Treatment B - Reference:** Moduretic, a hydrochlorothiazide 50mg and amiloride hydrochloride 5mg fixed dose combination.

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

A maximum of 42 participants will be randomized such that at least 32 evaluable participants complete the study.

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

If a subject is replaced, the replacement will be allocated the subject number of 500 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 subjects receive the same treatment sequence as the withdrawn subjects 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 bioequivalence study design.

## 5.5. Dose Justification

The doses of HCTZ (50 mg) and amiloride hydrochloride (5 mg) in GSK3542503 are well established and approved doses, marketed for treatment of hypertension, congestive heart failure or hepatic cirrhosis where ascites and oedema are present.

## 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 50 mg HCTZ/5 mg amiloride hydrochloride product information leaflet [**MODURETIC** Package Insert, 2015].

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. Participants must be between 18 and 65 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  $\geq$ 50 kilogram (kg) and body mass index (BMI) within the range 19-30kg/m<sup>2</sup>(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, for 3 days after each dose of study treatment and refrain from donating sperm during that 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](#) 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 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, or neurological disorders 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.
2. Abnormal renal function measured by creatinine clearance.
3. Presence of hyperkalaemia where the serum potassium is >ULN.
4. History or known acute angle closure glaucoma or ocular complaints which could increase the risk of ophthalmic reactions as deemed by the investigator .
5. Abnormal BP as determined by the investigator.
6. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
7. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
8. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
9. QT interval corrected for heart rate according to Bazett's formula (QTcB) >450 milliseconds (msec)

**NOTES:**

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

### **Prior/Concomitant Therapy**

10. Past or intended use of over-the-counter or prescription medication including herbal medications, within 14 days prior to dosing. Specific medications listed in Section 7.7 may be allowed.

### **Prior/Concurrent Clinical Study Experience**

11. Where participation in the study would result in loss of blood or blood products in excess of 500 mL within 90 days.
12. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
13. 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**

14. Presence of Hepatitis B surface antigen (HBsAg) at screening, or a positive Hepatitis C antibody test result at screening.

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

15. Positive pre-study drug/alcohol screen
16. Positive HIV antibody test
17. Regular use of known drugs of abuse

### **Other Exclusions**

18. Sensitivity to heparin or heparin-induced thrombocytopenia
19. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy including allergy to penicillin and sulphonamides that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.
20. 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.
21. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening.
22. Participants with any risk as described in Table 2 under Section 3.3.1, should be excluded from participation in this study.

### **6.3. Lifestyle Restrictions**

#### **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.
- Potassium rich foods should be avoided within 7 days of the first dose of study medication, and during participation in the study.
- 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.

#### **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. 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 serious adverse events (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
<b>Study Treatment Name:</b>	GSK3542503 / HCTZ / Amiloride Hydrochloride (BIDURET™)	Moduretic
<b>Dosage formulation:</b>	Tablet	Tablet
<b>Unit dose strength(s)/Dosage level(s):</b>	50 mg Hydrochloro-thiazide /5 mg Amiloride Hydrochloride	
<b>Route of Administration</b>	Route: oral Duration: single dose	
<b>Dosing instructions:</b>	1 tablet to be taken orally with 240 mL water.	
<b>Physical Description</b>	Cream-coloured, circular, flat faced uncoated tablet with bevelled edges having break line on one side and "BD" embossed on the other side	Peach-coloured, half scored, diamond shaped tablets marked "MSD917"
<b>Manufacturer / Supplier</b>	Manufactured by Panacea Biotec, India; supplied by GSK India, Mumbai.	Merck Sharpe & Dohme Limited, 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 GSK3542503 50 mg HCTZ/5 mg Amiloride Hydrochloride tablets (BIDURET<sup>TM</sup>)
- Treatment B – Reference 50 mg HCTZ/5 mg Amiloride Hydrochloride tablets (Moduretic)

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	21	Treatment A (GSK3542503)	Treatment B Reference
B-A	21	Treatment B Reference	Treatment A (GSK3542503)

### 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 (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in PAREXEL SOPs.
- 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 Medical Monitor should be contacted if there are any questions regarding concomitant or prior 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  $\leq 2$  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 Moduretic.

## **7.8. Treatment after the End of the Study**

Participants will not receive any additional treatment from GSK after completion of the study because only healthy participants are eligible for study participation.

# **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., activation or exacerbation of systemic lupus erythematosus)
- electrolyte imbalance
- hyperkalemia
- liver events (see Section 8.1.1).
- positive pregnancy test
- vomiting within  $2 \times$  the median  $t_{max}$  of the reference product

### **8.1.1. Liver Chemistry Stopping Criteria**

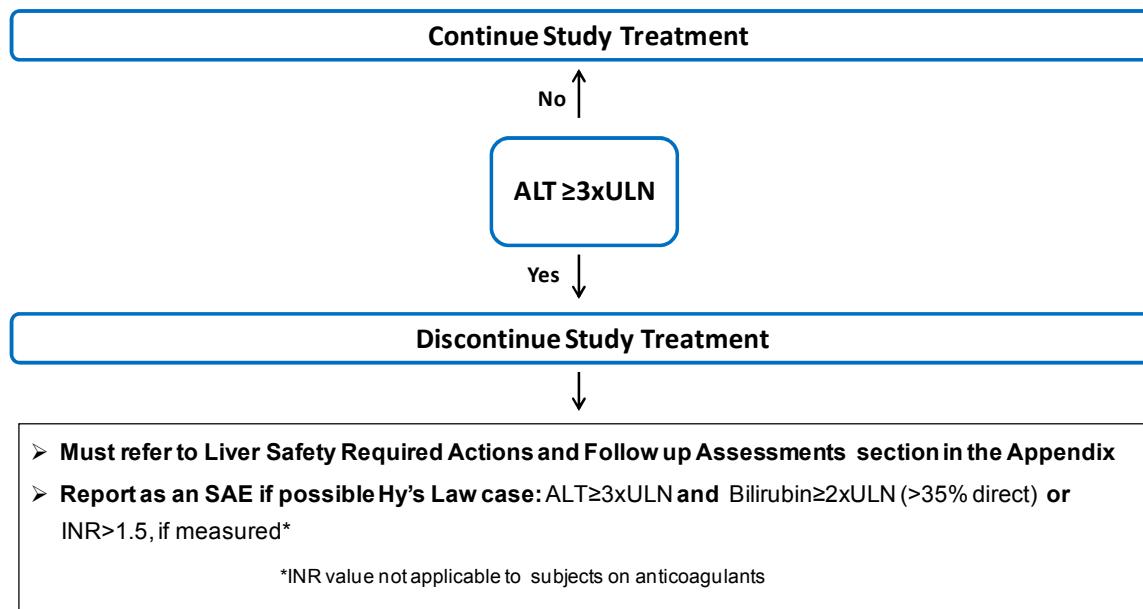
**Liver chemistry stopping and increased monitoring criteria** have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA 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 QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) 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 the bulleted criteria below will be withdrawn from study treatment.

- QTc, QTcB, >500 msec,
- Change from baseline: QTc >60 msec

### **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.

### 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).
- All AEs will be collected from the start of study treatment until the follow-up visit 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 SMPC 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 after the start of study treatment and until 3 days after the last dose or the follow up visit.
- 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 SAE.

#### **9.3. Treatment of Overdose**

For this study, any dose of study treatment GSK3542503 or comparator greater than 50mg HCTZ and 5mg Amiloride hydrochloride within a 24-hr time period will be considered an overdose.

The sponsor does not recommend any specific antidote as treatment for an overdose. Symptomatic and supportive treatment is recommended. Emesis should be induced and/or gastric lavage performed if warranted. 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 Hydrochlorothiazide and Amiloride 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  $\leq$  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  $\pm$  30 min.

### **9.4.3. Electrocardiograms**

- Single 12-lead ECG will be obtained at the Screening visit 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 report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- 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 etiology 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.
- Refer to the PAREXEL SOPs for appropriate processing and handling of samples to avoid duplicate/ and or additional blood draws.

#### 9.5. Pharmacokinetics

Pharmacokinetic sampling time-points are discussed in the SoA in Section [2](#).

- Whole blood samples of approximately 8 mL will be collected for measurement of plasma concentrations of HCTZ and amiloride 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 will be provided in the PAREXEL Bioanalytical Protocol. The actual date and time (24-hr clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of HCTZ and amiloride. Each plasma sample will be divided into 4 aliquots of not less than 700 µl plasma each (2 aliquots for the analysis of HCTZ and 2 aliquots for the analysis of amiloride). Samples collected for analyses of HCTZ and amiloride plasma concentration may

also be used to evaluate safety or efficacy aspects 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 0.33-24 hrs will be collected within 2 minutes
- Post dose samples for 36 and 48 hrs will be collected within 2 hrs
- 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 for the determination of multiple aspects of study treatments will be taken, 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 fixed dose tablet formulation GSK3542503 and the reference formulation, based on PK endpoints  $C_{max}$  and  $AUC_{(0-t)}$  of HCTZ and amiloride.

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  $C_{max}$ , and  $AUC_{(0-t)}$ , is either  $<0.80$  or  $>1.25$  for plasma HCTZ and amiloride.

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 the  $C_{max}$ , and  $AUC_{(0-t)}$ , is either  $\geq 0.80$  or  $\leq 1.25$  for plasma HCTZ and amiloride.

Symbolically this is expressed as follows:

$$H_0: \mu_{(Test)}/\mu_{(Reference)} < 0.80 \text{ or } \mu_{(Test)}/\mu_{(Reference)} > 1.25$$

i.e., treatments are not bioequivalent.

versus

$$H_a: 0.80 \leq \mu_{(Test)}/\mu_{(Reference)} \leq 1.25$$

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 HCTZ and amiloride.

### 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 both HCTZ and amiloride .

Due to unavailability of intra participant coefficient of variation ( $CV_w$ ) estimates in recent published data for amiloride , a more conservative intra participant  $CV_w$  of 23% is assumed [[MIDAMOR Package Insert, 2010](#)] . The variability of the primary endpoints of HCTZ was less than 20%, as per published data[[HPRA, 2015](#)] .

Hence, the sample size for this trial was determined based on maximum possible intra participant CV of 23%. Accounting for multiple BE assessments for HCTZ and amiloride, i.e. the overall power of the study is the product of the power of the test of HCTZ and amiloride.

Based on a BE range of 80.00% to 125.00% for  $C_{max}$  and  $AUC_{(0-t)}$ , for HCTZ and amiloride assuming intra participant CV to be not more than 23% and a "test/reference" mean ratio of 0.95; thirty two subjects are needed to achieve a power of 90% (in order to achieve an overall power greater than 80%) at an alpha level of 0.05 for the single test for testing BE.

Up to 42 eligible participants will be entered into the study to complete the study with at least 32 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 hydrochlorothiazide and amiloride 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 ( $C_{max}$ ), time to  $C_{max}$  ( $t_{max}$ ), area under the plasma concentration-time curve [ $AUC(0-\infty)$  and  $AUC_{(0-t)}$ ], and apparent  $t_{1/2}$  of hydrochlorothiazide and amiloride hydrochloride.

Participants who experience emesis during the course of the study may be deleted from the statistical analysis if vomiting occurred at or before 2 times median  $t_{max}$ . 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  $\leq 5\%$  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 GlaxoSmithKline (GSK).

Statistical analyses of the pharmacokinetic 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 PAREXEL Protocol Deviation Specification sheet.

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 hydrochlorothiazide and amiloride**

- 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 hydrochlorothiazide and amiloride**

- 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 ( $t_{1/2}$ )
- 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	<p>Following log-transformation of derived pharmacokinetic parameters <math>C_{max}</math> and <math>AUC_{(0-t)}</math> of hydrochlorothiazide and amiloride will be separately 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.</p> <p>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.</p> <p>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 seriously violated then alternative statistical methods will be considered.</p>
Secondary	<p><math>AUC_{(0-\infty)}</math> of HCTZ and amiloride will be analysed as per primary analysis; <math>t_{max}</math> of HCTZ and Amiloride 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</p> <p>%<math>AUC_{ex}</math> will not be statistically analysed. A summary will be created.</p> <p>For <math>t_{1/2}</math> the n, median, minimum, and maximum values will be presented</p>

### **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 (AEs) 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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## 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

23. Premenarchal

24. 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.

25. 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 enrollment.

#### 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 3 days after each dose of study treatment.
- Refrain from donating sperm for 3 days after each 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**

<b>Highly Effective Contraceptive Methods That Are User Dependent<sup>a</sup></b> <i>Failure rate of &lt;1% per year when used consistently and correctly.</i>	
Combined (estrogen- and progestogen-containing ) hormonal contraception associated with inhibition of ovulation <sup>b</sup>	
<ul style="list-style-type: none"> <li>• oral</li> <li>• intravaginal</li> <li>• transdermal</li> </ul>	
Progestogen-only hormonal contraception associated with inhibition of ovulation <sup>b</sup>	
<ul style="list-style-type: none"> <li>• injectable</li> </ul>	
<b>Highly Effective Methods That Are User Independent</b>	
<ul style="list-style-type: none"> <li>• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation<sup>b</sup></li> <li>• Intrauterine device (IUD)</li> <li>• Intrauterine hormone-releasing system (IUS)</li> <li>• bilateral tubal occlusion</li> </ul>	
Vasectomized partner	
<i>(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.)</i>	
Sexual abstinence	
<i>(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.)</i>	

## 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 fetal 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, by facsimile transmission to the **medical monitor / LOC Pharmacovigilance team** .
- 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, where applicable, and the IRB/IEC or study center.

- 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](http://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 15 years after study completion 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 etiology (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

Liver Chemistry Stopping Criteria	
<b>ALT-absolute</b> ALT $\geq$ 3xULN If ALT $\geq$ 3xULN AND bilirubin <sup>1,2</sup> $\geq$ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE. See additional Actions and Follow Up Assessments listed below	
Required Actions and Follow up Assessments	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> <li>Report the event to GSK <b>within 24 hours</b></li> <li>Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE<sup>2</sup></li> <li>Perform liver event follow up assessments</li> <li>Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see <b>MONITORING</b> below)</li> </ul> <p><b>MONITORING:</b></p> <p>If ALT<math>\geq</math>3xULN AND bilirubin <math>\geq</math> 2xULN or INR &gt;1.5</p> <ul style="list-style-type: none"> <li>Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within <b>24 hrs</b></li> <li>Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline</li> <li>A specialist or hepatology consultation is recommended</li> </ul>	<ul style="list-style-type: none"> <li>Viral hepatitis serology<sup>3</sup></li> <li>Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend</li> <li>Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 3 days of last dose</li> <li>Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</li> <li>Fractionate bilirubin, if total bilirubin<math>\geq</math>2xULN</li> <li>Obtain complete blood count with differential to assess eosinophilia</li> <li>Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form</li> <li>Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies,</li> </ul>

Liver Chemistry Stopping Criteria	
<p><b>If <math>ALT \geq 3 \times ULN</math> AND bilirubin &lt; <math>2 \times ULN</math> and INR <math>\leq 1.5</math>:</b></p> <ul style="list-style-type: none"> <li>Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within <b>24-72 hrs</b></li> <li>Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline</li> </ul>	<p>other over the counter medications.</p> <ul style="list-style-type: none"> <li>Record alcohol use on the liver event alcohol intake case report form</li> </ul> <p><b>If <math>ALT \geq 3 \times ULN</math> AND bilirubin <math>\geq 2 \times ULN</math> or INR <math>&gt; 1.5</math>:</b></p> <ul style="list-style-type: none"> <li>Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins.</li> <li>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]).</li> <li>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.</li> </ul>

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  $ALT \geq 3 \times ULN$  and  $bilirubin \geq 2 \times ULN$ . 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  $ALT \geq 3 \times ULN$  and  $bilirubin \geq 2 \times ULN$  ( $> 35\%$  direct bilirubin) or  $ALT \geq 3 \times ULN$  and  $INR > 1.5$ , if INR measured, which may indicate severe liver injury (possible 'Hys 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

### Definition of AE

AE Definition
<ul style="list-style-type: none"><li>• 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.</li><li>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.</li></ul>

### Events Meeting the AE Definition

<ul style="list-style-type: none"><li>• 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).</li><li>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</li><li>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li><li>• 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.</li></ul>
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### Events NOT Meeting the AE Definition

<ul style="list-style-type: none"><li>• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.</li><li>• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.</li><li>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that</li></ul>
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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 fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

#### **d. Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (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
<ul style="list-style-type: none"><li>When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.</li><li>The investigator will then record all relevant AE/SAE information in the CRF.</li><li>It is <b>not</b> 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.</li><li>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.</li><li>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.</li></ul>
Assessment of Intensity
<p>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:</p> <ul style="list-style-type: none"><li>Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.</li><li>Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.</li><li>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.</li></ul> <p>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.</p>

### 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.
- Facsimile transmission of the GSK SAE reporting form (paper) is the preferred method to transmit this information from the Investigator site to the **medical monitor** / LOC Pharmacovigilance team .
- 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 Pharmacovigilance 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 1](#) will 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 Indices: MCV MCH MCHC %Reticulocytes	WBC count with <u>Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry <sup>1</sup>	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	
	Chloride	Magnesium		
Coagulation Profile	<ul style="list-style-type: none"> <li>• PT and aPTT</li> </ul>			
Routine Urinalysis	<ul style="list-style-type: none"> <li>• Specific gravity</li> <li>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick</li> <li>• Microscopic examination (if blood or protein is abnormal)</li> </ul>			

Laboratory Assessments	Parameters
Other Screening Tests	<ul style="list-style-type: none"> <li>• Breath alcohol and urine drug screen (to include at minimum: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine (phenylcyclohexalpiperidine), tetrahydrocannabinol, methadone, methamphetamine, tricyclic antidepressants, oxycodone and propoxyphene)</li> <li>• Cotinine</li> <li>• Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)<sup>2</sup></li> <li>• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) Hepatitis C RNA test for Hepatitis C antibody positive Participants</li> </ul> <p>The results of each test must be entered into the CRF.</p>

## 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  $\geq 3 \times$  upper limit of normal (ULN) and bilirubin  $\geq 2 \times$  ULN ( $>35\%$  direct bilirubin) or ALT  $\geq 3 \times$  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 hydrochlorothiazide and amiloride per 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 hydrochlorothiazide and amiloride.

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  $\frac{1}{2}$ LLOQ 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  $\frac{1}{2}$ LLOQ, 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 hydrochlorothiazide and amiloride 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 hydrochlorothiazide and amiloride.

The individual plasma hydrochlorothiazide and amiloride concentration versus actual time profiles for each participant and treatment, as well as the mean (arithmetic and geometric) plasma hydrochlorothiazide and amiloride 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 individual log-linear graphs reflecting the WinNonlin modeling 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/GRAFH software<sup>1</sup>.

### **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

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<sup>1</sup> 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 7](#).

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 OverallANOVA=anova;
```

```
PROC GLM DATA=pk ALPHA=0.1;
```

```
BY Analyte Parameter;
```

```
CLASS treatment period participant sequence1
```

```
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;
```

---

<sup>1</sup>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 HCTZ PK parameters (ANOVA)

Statistical analyses of Amiloride PK parameters (ANOVA)

Plasma HCTZ concentration (unit)

Plasma Amiloride concentration (unit)

Adverse events summary by treatment

Concomitant Medication summary by treatment

Summary Statistics of Vital Signs Values

Summary Statistics of Chemistry Values.

### **Figures**

Plasma HCTZ arithmetic and geometric mean concentrations (unit)

Plasma Amiloride arithmetic and geometric mean concentrations (unit)  
Median concentration vs. Time for HCTZ and Amiloride  
Median concentration vs. Time for Amiloride  
Combined individual plasma HCTZ concentrations (unit)  
Combined individual plasma Amiloride concentrations (unit)  
Individual plasma HCTZ concentrations (unit) (linear-linear scale and log-linear scale)  
Individual plasma Amiloride concentrations (unit) (linear-linear scale and log-linear scale)  
Adjusted geometric mean treatment ratio (with 90% CI) for HCTZ and Amiloride

## **Listings**

Statistical output  
Participant disposition  
Randomization  
Demography and anthropometry  
Adverse events  
Concomitant Medication  
Vitals Signs  
Chemistry  
Actual blood sampling times  
Plasma HCTZ concentrations (unit)  
Plasma Amiloride concentrations (unit)  
Plasma HCTZ PK parameters (unit)  
Plasma Amiloride 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 $AUC(0-\infty)$ 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
HCTZ	Hydrochlorothiazide
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

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
t <sub>1/2</sub>	Terminal phase half-life
Tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
WBC	White blood cells
WCBP	Women of Childbearing Potential

### Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
BIDURET	Apo-amilizide Midamor Moduretic Phoenix SAS WinNonlin