

## TITLE PAGE

**Division:** Worldwide Development

**Information Type:** Protocol Amendment

<b>Title:</b>	A long term, randomised, double-blind, placebo-controlled study to determine the effect of albiglutide, when added to standard blood glucose lowering therapies, on major cardiovascular events in patients with Type 2 diabetes mellitus. Harmony Outcomes Trial
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2014N193553_01	2014-NOV-24	Amendment No. 1
<p>Clarification added regarding follow-up after discontinuation of investigational product.</p> <p>Addition of safety assessment to dose adjustment visits.</p> <p>Addition of Country Specific Requirements appendix.</p> <p>Correction of typographical errors and inconsistent terminology.</p>		
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<p>Amendment to study phase for participating countries where albiglutide is not licensed.</p> <p>Update list of Authors.</p> <p>Update to Sponsor Information</p> <p>Removal of discrepancy in level of pregnancy testing required for inclusion.</p> <p>Reformatting of Time and Event table to improve clarity.</p> <p>Addition of table of visits for subjects discontinuing investigational product (previously included in text) as an aid to investigators.</p> <p>Addition of requirement of Mexican Ministry of Health to report events referred to Clinical Endpoint Committee from Mexican investigators as Serious Adverse Events.</p> <p>Addition of requirement to record lipid results if they are available from subjects' routine clinical care outside of the trial.</p> <p>Clarify that TRIM-D should not be assessed at Baseline in subjects whose diabetes is treated by diet and exercise alone.</p> <p>Simplification of description of safety analyses to properly reflect the planned reports.</p> <p>Correction of typographical and process errors.</p>		
2014N193553_03	2017-APR-04	Amendment No. 3
<p>Addition of requirement that the study achieve a median subject follow up of at least 1.5 years as well as the sample size derived number of primary endpoints.</p> <p>Specifying that to meet the primary objective of assessing the effect of albiglutide with respect to MACE, the primary analysis will be non-inferiority. If the pre-specified non-</p>		

inferiority criterion is met then superiority testing will be performed with a closed testing procedure. Previously, superiority testing of MACE was considered a secondary endpoint.

Removal of multiplicity testing strategy for selected secondary endpoints.

Revision of the data collection strategy for the exploratory electronic healthcare record ancillary study (Appendix 7) with improved clarity for the planned data flow and analytical approach.

**SPONSOR SIGNATORY**

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4 APR 2017

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**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

For protocol number GLP116174

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

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## LIST OF ABBREVIATIONS

ACCF	American College of Cardiology Foundation
ADA	American Diabetes Association
AE	adverse event
AHA	American Heart Association
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANCOVA	analysis of covariance
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BI	baseline basal insulin population
BMI	body mass index
bpm	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEC	Cardiovascular Endpoint Committee
CI	confidence interval
CPK	creatinine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
DCRI	Duke Clinical Research Institute
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EHR	electronic health record
ESC	European Society of Cardiology
FDA	US Food and Drug Administration
FRP	females of reproductive potential
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GSK	GlaxoSmithKline
HbA1c	glycated haemoglobin
hCG	human chorionic gonadotrophin
HDLc	high density lipoprotein cholesterol
HLA	human leukocyte antigen
HRT	hormone replacement therapy
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normal range
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	Interactive Voice Response System

KM	Kaplan-Meier
LDH	lactate dehydrogenase
LFT	liver function test
LDLc	low density lipoprotein cholesterol
MACE	major adverse cardiovascular event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MSDS	Material Safety Data Sheet
MTC	medullary thyroid cancer
NHLBI	National Heart, Lung and Blood Institute
NI	non-insulin population
PAD	peripheral arterial disease
PD	pharmacodynamics
PHI	Protected Health Information
PK	pharmacokinetics
PP	per protocol
RAP	Reporting Analysis Plan
RR	relative risk
s.c.	subcutaneous
SAE	serious adverse event
SRM	Study Reference Manual
SU	sulfonylureas
TC	total cholesterol
Tg	triglycerides
TIA	transient ischemic attack
TRIM-D	Treatment Related Impact Measures-D
ULN	upper limit of normal range
WHF	World Heart Federation
WHO	World Health Organization

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## PROTOCOL SUMMARY

### Rationale

Albiglutide is a novel analogue of glucagon-like peptide-1 (GLP-1) with a sufficiently long half-life to permit once a week injection. Albiglutide is licensed for the treatment of type 2 diabetes as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies, including basal insulin. The Food and Drug Administration (FDA) has issued guidance on evaluating cardiovascular risk in new anti-diabetic therapies to treat type 2 diabetes [FDA [Guidance for Industry](#), 2008]. For a premarketing application that contains a meta-analysis of major adverse cardiovascular events (MACE) for which the upper bound of the 95 percent confidence interval for the relative risk is between 1.3 and 1.8, a post-marketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. The MACE meta-analysis of the albiglutide Phase III program (primary endpoint cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina), whilst ruling out an upper bound of the confidence interval for cardiovascular events of 1.8, was not able to rule out (due to a relatively small number of events) a relative risk (RR) upper bound of 1.3. For this reason GlaxoSmithKline (GSK) will conduct this cardiovascular outcome study as a US post-marketing requirement, to evaluate the effect of albiglutide on cardiovascular events in subjects with type 2 diabetes.

### Objectives/Endpoints

Objectives	Endpoints
<b>Primary</b>	
To assess the effect of albiglutide with respect to MACE when added to glycaemic standard of care versus standard of care alone	<p>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke)</p> <p>The primary analysis will be non-inferiority. If the pre-specified non-inferiority criterion is met then superiority testing will be performed <sup>1</sup></p>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start</li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li>The proportion of subjects achieving glycaemic control (HbA1c <math>\leq</math> 7.0% at final assessment) with no severe hypoglycaemic incidents and weight gain <math>&lt;5\%</math> of body weight</li> <li>The time to first occurrence of a clinically important</li> </ul>

Objectives	Endpoints
	microvascular event (see Section 6.2.4) <ul style="list-style-type: none"> <li>• Change in glycated haemoglobin (HbA1c)</li> <li>• Change in body weight</li> <li>• Patient reported outcomes from Treatment Related Impact Measures-D (TRIM-D)/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>• All cause mortality</li> <li>• Non-fatal serious adverse events (SAEs)</li> <li>• Adverse events (AEs) leading to discontinuation of investigational product</li> <li>• AE of special interest (see Section 6.2.3)</li> <li>• Change in estimated glomerular filtration rate (eGFR) calculated using Modification of Diet in Renal Disease (MDRD) formula</li> <li>• Change in blood pressure and heart rate</li> </ul>

1. As part of a closed testing procedure and therefore no adjustment will be made to the significance level (see Section 8.3.5)

## Overall Design

This is a randomised, double blind, parallel group, placebo-controlled study.

## Treatment Arms and Duration

All subjects will receive standard of care for their diabetes and cardiovascular health which can be adjusted by the healthcare professional responsible for the subject during the study according to clinical need and with close adherence to professional society treatment guidelines. The study comparison is thus between albiglutide added to standard of care and standard of care alone. Placebo injections will be used to ensure study assessments are performed without knowledge of treatment assignment. Treatment with albiglutide or placebo will be randomly allocated in a 1:1 ratio. The starting dose of albiglutide is 30 mg weekly which may be up-titrated to 50mg weekly if further improvement of glycaemic control is required.

The study will continue until it is projected that at least 611 adjudicated MACE events will have occurred while requiring that the projected median duration of subject follow-up be at least 1.5 years. The maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate. If 611 events are reached before the estimated median duration of subject follow-up is projected to be at least 1.5 years, then the study will continue until it is predicted that the median subject follow-up time is at least 1.5 years. In that case more than 611 events would likely be observed.

An Independent Data Monitoring Committee (IDMC) will have study oversight to ensure participant safety and scientific integrity of the data.

## Type and Number of Subjects

A total of 9400 subjects with type 2 diabetes and a previous history of cardiovascular disease and who do not have optimal glycaemic control will be studied.

**Analysis**

The study's primary question is whether albiglutide is non-inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. If non-inferiority is achieved, then superiority will be tested. The primary analysis is an Intent-to-Treat (ITT) analysis of the time to the first occurrence of MACE using Cox's Proportional Hazard regression.

## 1. INTRODUCTION

### 1.1. Background

Diabetes affects an estimated 347 million people worldwide, with type 2 diabetes accounting for more than 90% of cases [WHO, 2013]. The primary manifestation of this disease is chronic hyperglycaemia, resulting from resistance to insulin action at a cellular and molecular level and a relative inadequacy in the secretion of endogenous insulin [American Diabetes Association, 2014]. Chronic hyperglycaemia has been firmly established as a key factor in the development of microvascular complications (retinopathy, nephropathy, and neuropathy). Individuals with type 2 diabetes are also at greatly elevated risk of cardiovascular disease.

The management of glycaemia in individuals with type 2 diabetes consists of diet, exercise, and weight reduction together with oral anti-diabetic drug, injectable agents such as GLP-1 receptor agonists or insulin therapy, to achieve near normoglycaemia as reflected by a target HbA1c level of  $\leq 7\%$ , where possible, without significant hypoglycaemia or other adverse effects of treatment. Despite the large number of available therapeutic agents, a high proportion of subjects fail to achieve or maintain target HbA1c levels [Khunti, 2013] owing to the inexorable decline in endogenous insulin production characteristic of the disease, and limitations in existing treatments. New agents with complementary mechanisms (permitting combination use) or more favourable safety profiles are needed to help more subjects achieve glycaemic targets.

GLP-1 is secreted by intestinal L-cells in response to ingestion of food. In a healthy individual, it plays an important role regulating postprandial blood glucose by stimulating glucose-dependent insulin secretion by the pancreas. GLP-1 suppresses glucagon secretion, leading to reduced hepatic glucose output. It also delays gastric emptying time and slows small bowel motility, delaying food absorption and slowing the rate of glucose appearance in the blood. In patients with type 2 diabetes the postprandial rise in endogenous GLP-1 is absent or reduced [Vilsbøll, 2001].

GLP-1 receptor agonists have been developed as anti-hyperglycemic therapy for type 2 diabetes to replace or supplement endogenous GLP-1 in order to increase meal-related insulin secretion, reduce inappropriate glucagon secretion, and slow GI motility. They have demonstrated substantial effectiveness in improving glycaemic control while mitigating the risk of hypoglycaemia and weight gain commonly associated with some of the other treatments for type 2 diabetes [Stonehouse, 2012].

Albiglutide is a novel analogue of GLP-1 generated through a genetic fusion of 2 modified recombinant human GLP-1 molecules linked in tandem to recombinant human albumin. Albiglutide is licensed for the treatment of type 2 diabetes as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies (oral anti-diabetic therapies or basal insulin). It has been granted marketing authorisation by the European Medicines Agency (EMA) (March 2014) and the FDA (April 2014). Details of the clinical trial results can be found in the Investigator Brochure (IB).

## 1.2. Rationale

The FDA has issued guidance on evaluating cardiovascular risk in new anti-diabetic therapies to treat type 2 diabetes [FDA [Guidance for Industry](#), 2008]. For a premarketing application that contains a meta-analysis of MACE, for which the upper bound of the 95 percent confidence interval for the relative risk is between 1.3 and 1.8, a post-marketing trial may be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3.

The MACE + meta-analysis of the albiglutide Phase III program (primary endpoint cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina), whilst ruling out an upper bound of the confidence interval for cardiovascular events of 1.8, was not able to rule out (due to a relatively small number of events) a RR upper bound of 1.3. For this reason GSK will conduct this cardiovascular outcome study as a US post-marketing requirement, to evaluate the effect of albiglutide on cardiovascular events in subjects with type 2 diabetes.

Preclinical studies have provided evidence that GLP-1 receptor stimulation favourably effects endothelial function, recovery from ischemic injury, and myocardial function in animals [reviewed in [Okerson](#), 2012]. Albiglutide reduced infarct size assessed 24 hours after 30 minutes temporary left anterior descending coronary artery occlusion in normoglycaemic rats [[Bao](#), 2011]. GLP-1 infusion has been shown to improve endothelial function in subjects with stable coronary disease [[Nystrom](#), 2004]. In subjects with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, the GLP-1 receptor agonist, exenatide, administered at the time of reperfusion has been reported to increase myocardial salvage [[Lønborg](#), 2012]. In the Phase III studies, small mean increases in heart rate (1 to 2 bpm) and a higher incidence of atrial fibrillation/flutter events were observed with albiglutide. It is difficult to predict whether these preclinical and clinical findings will translate into effect on major cardiovascular events.



## 2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b>	
To assess the effect of albiglutide with respect to MACE when added to glycaemic standard of care versus standard of care alone	<p><b>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke)</b></p> <p>The primary analysis will be non-inferiority. If the pre-specified non-inferiority criterion is met then superiority testing will be performed<sup>1</sup></p>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start</li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li>The proportion of subjects achieving glycaemic control (HbA1c <math>\leq 7.0\%</math> at final assessment) with no severe hypoglycaemic incidents and weight gain <math>&lt;5\%</math> of body weight</li> <li>The time to first occurrence of a clinically important microvascular event (see Section 6.2.4)</li> <li>Change in HbA1c</li> <li>Change in body weight</li> <li>Patient reported outcomes from TRIM-D/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>All cause mortality</li> <li>Non-fatal SAEs</li> <li>AEs leading to discontinuation of investigational product</li> <li>AE of special interest (see Section 6.2.3)</li> <li>Change in eGFR calculated using MDRD formula</li> <li>Change in blood pressure and heart rate</li> </ul>
<b>Exploratory</b>	
To evaluate patient reported experience of diabetes treatment	<ul style="list-style-type: none"> <li>Patient reported outcomes from study specific questionnaire</li> </ul>
To evaluate (at a subset of sites) barriers to using the electronic health record (EHR) to facilitate trial enrolment and the quality of	<ul style="list-style-type: none"> <li>Workflow impact of an EHR-generated list of subjects to facilitate trial enrolment.</li> <li>Concordance, sensitivity, specificity, and accuracy of baseline characteristics extracted from the EHR compared with those reported on the electronic case report form (eCRF)<sup>3</sup></li> </ul>

Objectives	Endpoints
EHR data for use in populating baseline characteristics and identifying events of interest during trial follow-up. <sup>2</sup>	<ul style="list-style-type: none"> <li>Concordance, sensitivity, specificity, and accuracy of EHR-identified events compared with study events <sup>3,4</sup></li> </ul>

- As part of a closed testing procedure and therefore no adjustment will be made to the significance level (see Section 8.3.5)
- Details are provided in a separate EHR ancillary study protocol (Appendix 7). Results from this exploratory investigation will be reported separately from the main clinical study report.
- Comparison of EHR identified events with study events will be conducted in the same data subset.
- Analyses to be undertaken after the main trial results are published.

### 3. STUDY DESIGN

#### 3.1. Overall Design

This is a randomised, double blind, parallel-group, placebo-controlled, multicentre study. In countries where marketing authorization has been granted to albiglutide for the treatment of type 2 diabetes it is classified as a Phase IV study, elsewhere it should be considered to be a Phase III study. This study will recruit approximately 9400 subjects with type 2 diabetes and a previous history of cardiovascular disease who are failing to achieve optimal glycaemic control on their current anti-hyperglycaemic regimen. Subjects will be randomised in a 1:1 ratio to albiglutide or albiglutide matching placebo administered once weekly by subcutaneous (s.c.) injection.

All subjects will receive standard of care which can be adjusted by their usual care provider(s) during the study according to clinical need (See Section 3.2). The study comparison is between albiglutide added to standard of care and standard of care alone.

The starting dose of albiglutide will be 30 mg once weekly. If at any stage after 5 weeks of treatment the subject needs to have intensified therapy to improve glycaemic control, the dose of investigational product should be increased before altering the doses of or adding other glucose-lowering medication. This treatment decision will be the responsibility of the investigator. In this case the subject will be called in for an unscheduled visit to increase the dose from 30 mg to 50mg. Subjects randomly assigned to albiglutide matching placebo will also go through the increased dose procedure to maintain study blind. If a subject experiences tolerability issues with the higher, 50mg dose then the investigator may decrease the dose back to 30 mg without the need for an unscheduled visit to supervise down titration. Use of GLP-1 receptor agonists will be prohibited but other glucose-lowering medications permitted, provided they are not contraindicated for the individual subject concerned.

This study is designed with minimal intervention above normal clinical care of subjects with type 2 diabetes, whilst allowing thorough evaluation of cardiovascular and other events of special interest (Section 6.2.3), thus investigating the safety of albiglutide in the typical clinical situation. Sites will employ pre-screening to assess potential subjects for study entry. Screening and randomisation can then occur at the same visit or in close proximity depending on scheduling. Contact with subjects will be every four months

after the randomisation visit. HbA1c will be measured at 4 month clinic visits. Serum creatinine and liver function tests (LFTs) will be measured and a targeted physical assessment performed at 8 month clinic visits (Table 1).

The study will continue until it is projected that at least 611 adjudicated MACE events will have occurred while requiring that the projected median duration of subject follow-up be at least 1.5 years. The maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate, and was originally estimated to be between 3 and 5 years. If the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years, respectively. If the observed rate for MACE is sufficiently high such that the median subject follow-up would be less than 1.5 years then the study will continue until it is projected that the median follow-up is at least 1.5 years. In this scenario, the maximum duration of the study for an individual participant would be less than the 3 to 5 years originally estimated.

An Executive Committee will be the main decision-making body for the study, in collaboration with the Sponsor (GSK). It is charged with the overall scientific, professional and operational conduct of the study. Amongst other roles pre-specified in its Charter, the Executive Committee will ensure proper study conduct and conformance to the protocol, consider and agree changes to the protocol based on emerging scientific and/or clinical advances (e.g., new emerging data with other GLP-1 receptor agonists), advise on the selection of study sites and assist in subject recruitment strategies.

An IDMC will have study oversight to ensure participant safety and scientific integrity of the data (Section 9.8), an independent Cardiovascular Endpoint Committee (CEC) blinded to treatment allocation will adjudicate cardiovascular outcome events (Section 6.2.1) and a Pancreatitis Adjudication Committee will adjudicate potential events of pancreatitis.

Subject completion is defined as completion of all periods of the study up to and including any follow-up period.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 1), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

### **3.2. Standard of Care**

Anti-hyperglycaemic and cardiovascular medications will be used at the discretion of the usual care provider(s) (or investigator if also the usual care provider), who will be informed of the patient's enrolment in the trial, the use of blinded trial medication, and that use of GLP-1 receptor agonists (other than the use of randomised albiglutide) is contraindicated during the trial period. Usual care providers will be encouraged to follow

the most up to date guidelines for diabetes and cardiovascular care based upon local and institutional practice patterns and any relevant published practice guidelines (e.g., [Inzucchi, 2012](#)). Treatment for type 2 diabetes will be captured by name and total daily dose at the time of study visits, while other relevant (cardiovascular) concomitant medications will be collected only as drug classes (see Section [5.6.1](#)).

During the study investigators are expected to monitor patients' type 2 diabetes regimens and communicate with usual care providers, who will be responsible for adjusting their regimen in order to achieve locally-appropriate HbA1c goals. The Executive Committee and National Country Leaders will encourage investigators to follow clinical care practice guidelines published by national and international societies regarding type 2 diabetes over the course of the trial. These practice guideline goals will be individualized, with the understanding that currently applicable glycaemic guidelines may vary among different geographic regions. With adherence to local custom and laws (including privacy regulations such as the Health Insurance Portability and Accountability Act), types of communication may be informal e.g. email or telephone exchanges, to enhance frequency and ease of two-way communication.

Any agent, with the exception of GLP-1 receptor agonists, is acceptable for reaching HbA1c goals. If HbA1c goals are not met following adjustment with oral medications in patients not receiving insulin, an insulin regimen may be initiated. Patients already receiving insulin therapy may up-titrate insulin during the trial if necessary. Patients should be reminded to keep taking their blinded trial medication throughout the course of the trial even in the case after initiation of insulin.

The Executive Committee and National Country Leaders will also monitor the standard of care of management of diabetes and cardiovascular disease. Similar to the management of type 2 diabetes, sites and investigators will be expected to adhere to local clinical practice guidelines. Sites will be provided training on clinical management guidelines to re-enforce standard of care adherence. Information on medications important to management of cardiovascular risk will be captured during study visits. The Executive Committee and National Country Leaders will review on a periodic basis the use of medications for cardiovascular risk prevention to ensure patients are receiving standard of care. If there are unusually low goal attainments for standard of care, site investigators will be advised accordingly.

### **3.3. Discussion of Design**

This study is a clinical outcomes trial required by FDA as a post-marketing requirement to evaluate cardiovascular safety. It will provide important information regarding the cardiovascular safety and metabolic effects of albiglutide treatment of subjects with type 2 diabetes. Sufficient MACE events must be observed during the study to permit the assessment of cardiovascular safety. Consequently, to enter the study subjects must have established cardiovascular disease as well as type 2 diabetes. The study is powered on a predefined number of clinical events, consequently the number of subjects required and study duration may vary from that stated in the protocol.

This will be a double-blind, placebo-controlled study. All subjects will receive placebo or albiglutide in addition to usual standard of care for type 2 diabetes and cardiovascular disease, in order to assess the effect of albiglutide above that of currently available therapies alone.

The primary cardiovascular comparison will be to assess whether albiglutide is non-inferior to placebo with respect to time to first MACE. If non-inferiority is established, the time to first MACE for albiglutide compared to placebo will be tested for superiority. Missing data may inappropriately bias comparison towards declaring non-inferiority. The longer the duration of a study, the more difficult it is to avoid loss to follow-up and other sources of missing data. The product of the projected duration of this study and the number of subjects to be studied is intended to minimize the risk of missing data whilst still permitting the assessment of the safety of albiglutide to be over an appreciable period of time. Every effort will be made to keep subjects on their assigned study medication according to the protocol. Subjects who stop study medication will be followed throughout the whole study duration. More details about procedures for subject follow-up are provided in Section 4.5.

Phase III studies confirmed the glycaemic efficacy of both 30 mg and 50 mg doses of albiglutide, and both were generally well-tolerated. Although the 30 mg dose was effective at controlling glycaemia for at least 2 years in many subjects with type 2 diabetes, an increase in dose to 50 mg weekly offered additional benefit without significant safety issues (See IB for further details).

### **3.4. Benefit:Risk Assessment**

Albiglutide has been evaluated in an international programme of studies involving approximately 9000 subject-years of overall exposure to date (including over 4000 subject-years of exposure to albiglutide). The programme included 8 well-controlled Phase III studies (including one in subjects with concurrent renal impairment), ranging in duration from 32 weeks to 3 years, and using both 30 mg and 50 mg once weekly dosing. This has permitted a thorough assessment of efficacy, safety, and tolerability in a population of subjects with type 2 diabetes that spanned newly diagnosed individuals treated with diet and exercise alone through to subjects on background oral monotherapy, oral dual therapy, oral triple therapy, and basal insulin.

Summaries of findings from both clinical and non-clinical studies conducted with albiglutide can be found in the IB and in the product labelling for those countries where marketing authorisation has been granted. The following section outlines the risk assessment and mitigation strategy for this protocol:

#### **3.4.1. Risk Assessment**

The identified and potential risks associated with the use of albiglutide, or the GLP-1 receptor agonist class, as well as the mitigation strategy for key risks of clinical significance are provided below. Please refer to the IB for a thorough summary of the nonclinical and clinical experience with albiglutide as well as the complete Guidance for the Investigator. The risks associated with study comparator, placebo, are also provided

below. Subjects will have the AE profile of GLP-1 receptor agonists, and albiglutide in particular, explained to them by the investigator and via the informed consent form.

#### **3.4.1.1. Identified Risks**

**Pancreatitis.** Acute pancreatitis has been reported in association with albiglutide and other GLP-1 receptor agonists in clinical trials and during postmarketing experience. Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether they are at increased risk for pancreatitis. Subjects with a history of pancreatitis or who are considered at significant risk of developing pancreatitis are excluded from entering the study. Subjects will be informed of the characteristic symptom of pancreatitis: persistent severe abdominal pain. If pancreatitis is suspected, investigational product should be promptly discontinued and if pancreatitis is confirmed, investigational product will not be restarted.

**Gastrointestinal events.** Albiglutide has not been studied in subjects with severe gastrointestinal (GI) disease, including severe gastroparesis. Subjects with severe gastroparesis will be excluded from the study. Use of albiglutide and other GLP-1 receptor agonists can be associated with GI side effects such as diarrhoea, nausea, and vomiting; the frequency of these events increased as renal function decreased. These types of GI reactions can be associated with dehydration and worsened renal function. (see below and see Section 4.4.4). Other GI related adverse reactions with albiglutide include dyspepsia, gastro-oesophageal reflux disease and constipation.

**Hypoglycaemia.** Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycaemia. However, when used in combination with insulin (or insulin secretagogues) the risk of hypoglycaemia is increased. Investigators will be reminded that it may be necessary to reduce the dose of insulin or insulin secretagogues when starting study medication to reduce the risk of hypoglycaemia. Routine standard of care for subjects treated with insulin secretagogues and insulin includes advice about avoidance of hypoglycaemia which will be reinforced. All subjects are required to have a last indicator of glycaemic control of above HbA1c = 7% which is expected to reduce the risk of hypoglycaemia when starting albiglutide.

**Immunogenicity.** Hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III programme. In the Phase III programme one subject (anti-albiglutide antibody negative) developed rash, itching and dyspnoea. Subjects with known allergy to any GLP-1 receptor agonist or excipients of albiglutide are excluded from the study. Subjects will be informed of the symptoms of severe hypersensitivity or allergy and be advised to seek medical assistance immediately. In the Phase III programme approximately 5% of subjects developed anti-albiglutide antibodies. Subjects who tested positive for anti-albiglutide antibodies experienced a similar glycaemic response (HbA1c and fasting plasma glucose) to those who did not test positive for antibodies. Other than injection site reactions (see below), the overall safety profile appeared similar among the subset of subjects who did and those who did not test positive for anti-albiglutide antibodies. Anti-albiglutide antibody formation is not expected to impact the overall safety of albiglutide treatment and therefore will not be measured routinely in this study.



**Injection site reactions.** Albiglutide injections may cause rash, erythema or itching and/or other reactions at the site of injection. . Subjects will be advised that when injecting in the same region, to use a different injection site each week. In the Phase III program, most subjects with injection site reactions did not test positive for anti-albiglutide antibodies. However, injection site reactions were reported more frequently among those who did test positive for anti-albiglutide antibodies (41% of the antidrug antibody positive subjects reported one or more injection site reactions) than among those who were consistently antibody negative (14% of the antidrug antibody negative subjects reported one or more injection site reactions).

**Other adverse reactions** (e.g. pneumonia, atrial fibrillation/flutter, and appendicitis). In the Phase III programme in type 2 diabetes, other possible albiglutide related adverse reactions were identified. These events occurred at a cumulative incidence <3% in studies up to 3 years in duration. These events were reported more frequently with albiglutide than comparators.

#### **3.4.1.2. Potential Risks**

**Thyroid C-cell tumours.** GLP-1 receptor agonists, including albiglutide increase serum calcitonin in rodents and other GLP-1 receptor agonists are associated with thyroid C-cell focal hyperplasia and C-cell tumours in rodents. It is unknown whether GLP-1 receptor agonists are associated with thyroid C-cell tumours in humans, including medullary thyroid cancer (MTC). Subjects with a personal or family history of MTC or subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) are excluded from the study. Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. Routine monitoring of serum calcitonin is not recommended. However, if serum calcitonin is found to be elevated the subject should be referred to a specialist for further evaluation. If MTC or other thyroid C-cell neoplasia is diagnosed, investigational product will be discontinued.

**Other malignant neoplasms** Concerns have been raised regarding use of incretin based therapies and other malignancies such as pancreatic cancer [[Egan, 2014](#)], malignancy when used in combination with insulin based on hypotheses of biological plausibility [[European Public Assessment Report, 2014](#)], and haematological malignancies [[FDA Summary Basis of Approval, 2014](#)].

**Hepatotoxicity.** Hepatotoxicity is an area of interest in drug development. Patients with type 2 diabetes are at increased risk for liver enzyme abnormalities and disease related liver conditions. One subject treated with albiglutide in the Phase III clinical programme developed probable drug induced liver injury with an asymptomatic elevation in alanine amino transferase (ALT) and total bilirubin although the cases had some atypical features and complicating factors. Routine liver safety laboratory evaluations will be conducted and specific withdrawal criteria for elevated liver function tests have been defined (See Section [4.4.3](#)).

**Subject population with severe renal impairment (eGFR <30 mL/min/1.73m<sup>2</sup>).** Experience in type 2 diabetes subjects with severe renal impairment is limited (in the Phase III programme a total of 19 subjects with eGFR <30 mL/min/1.73m<sup>2</sup> received albiglutide).

In a Phase 3 study of patients with varying degrees of renal impairment, in the albiglutide group, on-therapy GI AEs occurred with a higher incidence and higher event rate in subjects with moderate and severe renal impairment compared to those with mild renal impairment. Because these GI events may lead to dehydration and worsen renal function, worsening renal function will be closely evaluated as an AE of special interest, serum creatinine will be measured every 8 months, and subjects will discontinue IP if eGFR falls below 15 mL/min/1.73m<sup>2</sup>. Subjects with known severe renal impairment are excluded from the study (see Section 4.4.4).

**Drug Interactions.** Like other members of the class, albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the development programme, drug interactions studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant PK or PD effects. Investigators will be advised to take the effect of albiglutide on gastric emptying into account when prescribing concomitant medication.

**Pregnancy and Lactation.** Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. It is not known if albiglutide is secreted into human milk during lactation. Given that albiglutide is an albumin-based protein therapeutic, it is likely to be present in human milk. Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation. Subjects who are breastfeeding, pregnant or planning a pregnancy during the course of the study are excluded. Additionally, all females of child-bearing potential must be taking adequate contraception during the study and have a negative pregnancy test prior to entry.

**Placebo control.** In subjects treated with placebo, symptoms and long-term risks of hyperglycaemia may not improve or may worsen. During the study, intensification of glucose-lowering treatments other than study drug will be allowed in both treatment arms with a treat-to-target approach. Albiglutide placebo injections may cause injection site reactions. Subjects will be advised when injecting into the same region to use a different injection site each week.

### 3.4.2. Benefit Assessment

In subjects with type 2 diabetes albiglutide treatment resulted in clinically relevant lowering of HbA1c at both the 30 mg and 50 mg doses when given as monotherapy and in combination with metformin, sulfonylureas (SUs), thiazolidinedione or basal insulin. The durability of the effect on glycaemic control was shown over a study period of up to 3 years. Consistent with its mechanism of action, albiglutide was not associated with clinically relevant hypoglycaemia except when used in combination with an SU or insulin, and incidence rates with the combination were less than those reported with SUs or insulin alone. Treatment with albiglutide generally produced a steady reduction in weight over time.

For subjects not yet on insulin at the start of the study, data from the Phase III programme suggest that the use of albiglutide once weekly in a pen device may have the potential to delay the need to start daily insulin injections. This will be formally assessed within this trial. Similarly, it is possible that for those already taking basal insulin, albiglutide may



delay the need to introduce short-acting prandial injections and for those taking basal/bolus or pre-mixed insulin, it may reduce the dosage of insulin and/or the number of daily injections needed to achieve good glycaemic control. These will also be evaluated in the study.

Subjects in the placebo arm will also be receiving effective anti-hyperglycaemic medication which will be titrated up or down as required to improve or maintain glycaemic control, and therefore these subjects should also demonstrate reductions in HbA1c, though weight gain (rather than weight loss) may occur depending upon the medication selected.

Finally, as a result of participating in a clinical trial, each subject will receive more contact with the study site than would be performed as part of their usual standard of care.

### **3.4.3. Overall Benefit:Risk Conclusion**

Taking into account the measures taken to minimise risk to subjects participating in this study, the known and potential risks identified with albiglutide are justified by the benefits have been demonstrated in subjects with type 2 diabetes.

## **4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA**

### **4.1. Inclusion Criteria**

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB for albiglutide and in the product label for those countries where marketing authorisation has been granted.

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

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

1. Men or women at least 40 years old with a diagnosis of type 2 diabetes.
2. Established cardiovascular disease, including at least 1 of the following:
  - a. Coronary artery disease with EITHER of the following:
    - Documented history of spontaneous myocardial infarction, at least 30 days prior to Screening.
    - Documented coronary artery disease (CAD)  $\geq$  50% stenosis in 1 or more major epicardial coronary arteries, determined by invasive angiography, or history of surgical or percutaneous (balloon and/or stent) coronary revascularization procedure (at least 30 days prior to Screening for

percutaneous procedures and at least 5 years prior to Screening for coronary artery bypass graft (CABG)).

- b. Cerebrovascular disease – ANY of the following:
  - Documented history of ischaemic stroke, at least 90 days prior to study entry.
  - Carotid arterial disease with  $\geq 50\%$  stenosis documented by carotid ultrasound, magnetic resonance imaging or angiography, with or without symptoms of neurologic deficit.
  - Carotid vascular procedure (e.g. stenting or surgical revascularisation), at least 30 days prior to Screening.
- c. Peripheral arterial disease (PAD) with EITHER of the following:
  - intermittent claudication and ankle:brachial index  $< 0.9$  in at least one ankle
  - prior non-traumatic amputation, or peripheral vascular procedure (e.g. stenting or surgical revascularisation), due to peripheral arterial ischaemia.
3. HbA1c  $>7.0\%$  (53 mmol/mol) based on the most recent documented laboratory assessment measured no more than 6 months prior to randomization. Local laboratory HbA1c values taken as part of usual care are permitted.
4. Female: subject is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test for females of reproductive potential only), not breastfeeding, and at least one of the following conditions applies:
  - a. Reproductive potential and agrees to follow one of the options listed in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (e.g. combined oral contraceptive pill; see [Appendix 2](#)) from 30 days prior to the first dose of study medication and until after the last dose of study medication and completion of the follow-up visit.

This does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent. Other situations in which contraception in FRP may not need to be mandated should be discussed with the Medical Monitor.
  - b. Non-reproductive potential defined as either:
    - Pre-menopausal with one of the following: (i) documented tubal ligation; (ii) documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion; (iii) hysterectomy; or (iv) documented bilateral oophorectomy, or;
    - Postmenopausal defined as 12 months of spontaneous amenorrhea and age appropriate (i.e.  $>50$  years). In questionable cases, a blood sample with simultaneous follicle stimulating hormone (FSH)  $>40$  mIU/mL and oestradiol  $<40$  pg/mL ( $<140$  pmol/L) is confirmatory, depending on local laboratory ranges. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective

contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

5. Able and willing to provide informed consent.

## **4.2. Exclusion Criteria**

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

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

1. eGFR calculated using MDRD formula  $<30\text{mL}/\text{min}/1.73\text{m}^2$  (based on the most recent documented serum creatinine laboratory assessment measured no more than 6 months prior to randomization. Local laboratory creatinine values taken as part of usual care are permitted) or renal replacement therapy.
2. Use of a GLP-1 receptor agonist at Screening.
3. Severe gastroparesis requiring therapy within 6 months prior to Screening.
4. History of pancreatitis or considered clinically at significant risk of developing pancreatitis during the course of the study (e.g. due to symptomatic gallstones, excess alcohol use).
5. Personal or family history of medullary carcinoma of the thyroid or subject with MEN-2. Personal history of pancreatic neuroendocrine tumours. In the opinion of the investigator, the subject has a medical history which might affect his / her ability to remain in the study for its entire duration, or which might limit management, such as life expectancy of  $<5$  years (e.g. due to active malignancy).
6. Subject has a medical history which in the opinion of the investigator might limit the individual's ability to take trial treatments for the duration of the study or to otherwise complete the study.
7. Breastfeeding, pregnancy, or planning a pregnancy during the course of the study. Pregnancy test will be required in women of child bearing potential. Women who have undergone a sterilisation procedure or who are clearly post-menopausal will not be required to undergo pregnancy testing. Women who have developed spontaneous secondary amenorrhoea of 12 months or more where post-menopausal status is in doubt, a blood sample where FSH  $>40\text{MU}/\text{ml}$  and oestradiol  $<40\text{pg}/\text{mL}$  ( $<140\text{pmol}/\text{L}$ ) are simultaneously measured will be considered confirmatory.
8. Known allergy to any GLP-1 receptor agonist or excipients of albiglutide.
9. Use of another investigational product within 30 days or according to local regulations, or currently enrolled in a study of an investigational device.

10. Any other reason the investigator deems the subject to be unsuitable for the study.

### **4.3. Screening/Baseline Failures**

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements [Schulz, 2010], and respond to queries from regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any SAEs.

Re-screening of subjects who did not meet the eligibility criteria for HbA1c or creatinine based on local laboratory values taken as part of usual care is permitted. If values were based on laboratory results as part of usual care then one re-test is permitted within the protocol at Screening. Any future re-screening will be based on laboratory results obtained as part of usual care.

### **4.4. Criteria for Early Discontinuation of Investigational Product**

The primary analysis will be conducted on an ITT analysis basis so it is important that every subject is followed for the duration of the study, regardless of whether the subject continues to take investigational product, unless consent for all follow up is actively withdrawn.

The requirements for handling early discontinuations from investigational product are described below. Details of the requirements for subject follow-up are provided in Section 4.5.

#### **4.4.1. Early Discontinuation of Investigational Product**

If a subject chooses to discontinue investigational product between scheduled face-to-face visits they should be encouraged to contact the investigator site by telephone. Subjects should first be counselled to consider temporary discontinuation of investigational product prior to choosing to discontinue investigational product permanently, unless the reason for discontinuation is one of those listed below (Reasons for Discontinuation of Investigational Product). If the discontinuation is permanent, the subject should be asked to attend the clinic as soon as possible to complete the assessments as for the final study visit (see Table 1) and then continue in the study for follow-up. The procedures for follow-up for a subject who permanently discontinues treatment with investigational product prior to the study end are given in Section 4.5.

In all cases, reasons for discontinuation of investigational product and the date of last dose will be recorded.

#### 4.4.2. Reasons for Discontinuation of Investigational Product

Any subject experiencing the following will be required to discontinue investigational product:

AE:

- Pancreatitis, acute or chronic.

- Pancreatic cancer.

- MTC or other thyroid C-cell neoplasia. In subjects where a treatment emergent thyroid nodule is identified, if serum calcitonin is measured at the discretion of the Investigator (e.g., per local guidelines) and found to be >100 ng/L this should prompt further investigation for MTC and potential interruption or discontinuation of investigational product until diagnosis has been resolved.

- Liver chemistry abnormalities exceeding the threshold criteria outlined in Section 4.4.3

- Severe allergic/hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology.

- Other AE which, in the opinion of the investigator precludes continuation of dosing.  $eGFR < 15 \text{ ml/min/1.73m}^2$  (Section 4.4.4) or the need for renal replacement therapy.

- Subject becomes pregnant during the study.

- Need for chronic use of a prohibited concomitant medication (Section 5.6.2)

- Decision by subject or proxy.

- Sponsor terminated study.

Investigator site closed and subject was unable to transfer to another investigative site.

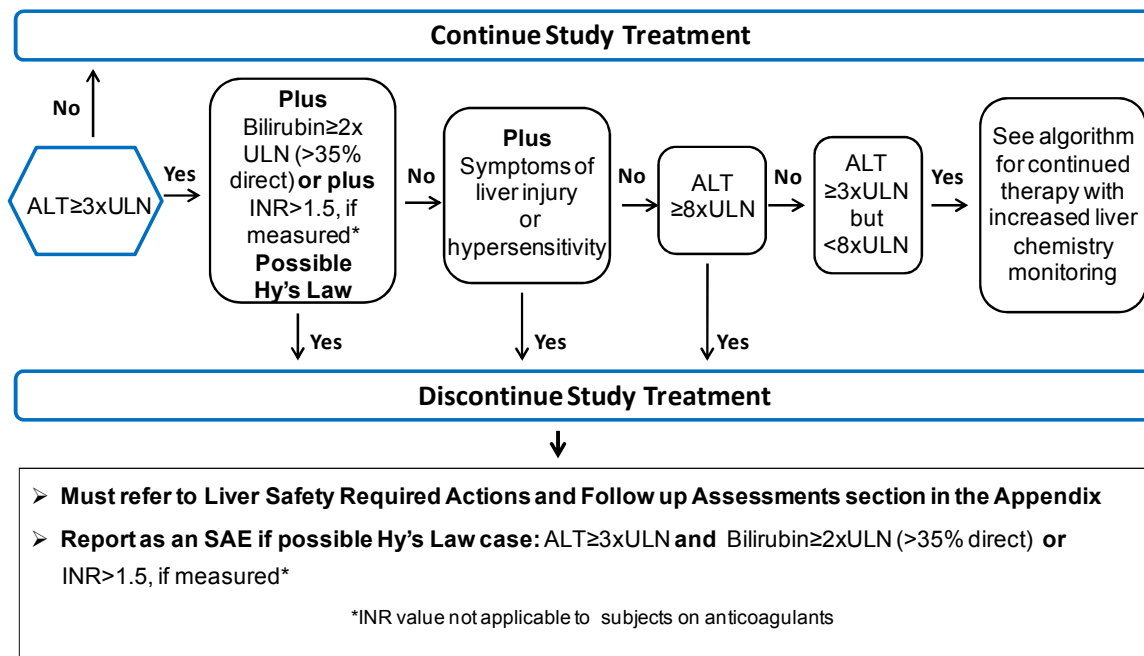
If investigational product is discontinued, the subject should continue in the study and be followed until the final study visit as detailed in Section 4.5.

#### 4.4.3. Liver Chemistry Stopping Criteria

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

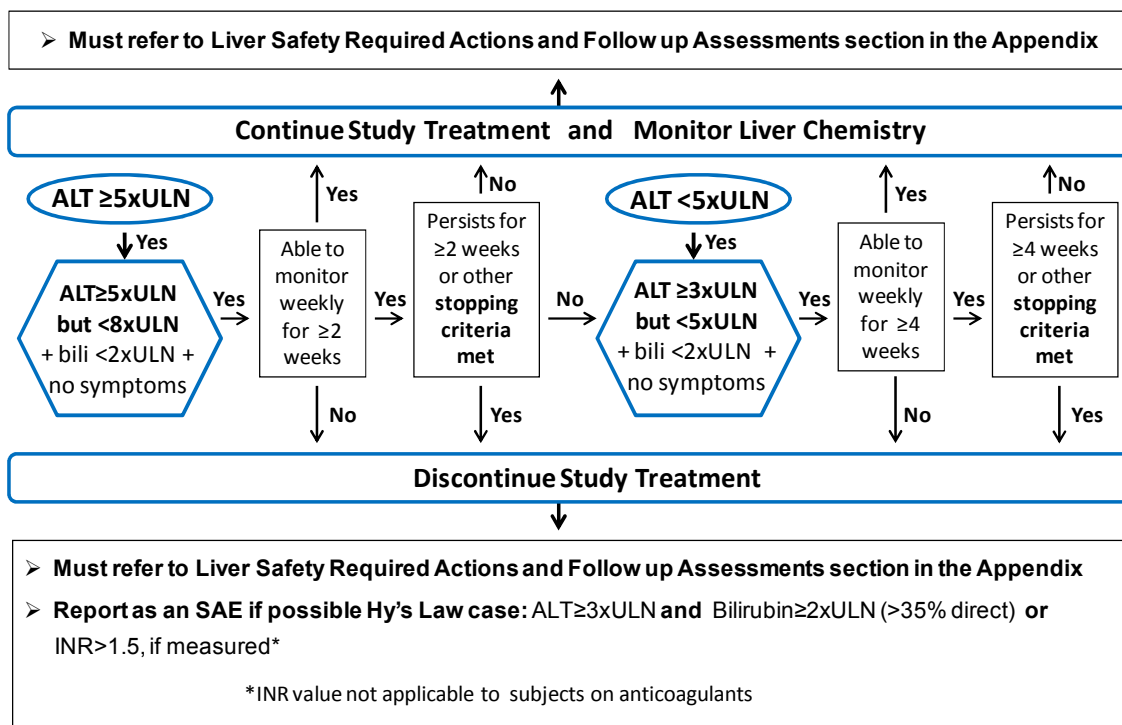
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

#### Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver safety required actions and follow up assessments section can be found in [Appendix 3](#).

### Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3xULN$ but $< 8xULN$



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 3](#).

Drug re-challenge following drug induced liver injury is not allowed.

Restart may be considered if GSK Medical Governance approval is granted (see [Appendix 4](#) for details). Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with human leukocyte antigen (HLA) markers of liver injury.

#### 4.4.4. eGFR Stopping Criteria

A baseline eGFR  $\geq 30\text{mL}/\text{min}/1.73\text{m}^2$  is a requirement for entering the study. Subjects can continue to take investigational product if functioning well as long as eGFR is  $\geq 15\text{mL}/\text{min}/1.73\text{m}^2$ .

During this study, if a subject's eGFR approaches  $30\text{mL}/\text{min}/1.73\text{m}^2$  closer monitoring of renal function is considered prudent, according to standard clinical practice. Particular

care should be taken to monitor renal function in subjects with renal impairment reporting severe adverse GI events. If eGFR is  $<15\text{mL}/\text{min}/1.73\text{m}^2$  and considered irreversible based on consecutive measurements the investigational product should be discontinued, the subject continue in the study and be followed until the final study visit.

If eGFR is  $<15\text{mL}/\text{min}/1.73\text{m}^2$  and the patient is considered to have temporary acute kidney injury that is potentially reversible, the investigational product should be temporarily discontinued until the eGFR is stable and  $\geq 15\text{mL}/\text{min}/1.73\text{m}^2$ . Events considered to reflect worsening renal function should be reported as SAE/AEs and targeted eCRFs completed for this AE of special interest (Section 6.2.3).

#### **4.5. Procedures for Subject Follow-up**

As described in Section 4.4, subjects who permanently discontinue investigational product will be asked to attend the clinic as soon as possible. They will continue in the study for follow-up. Five weeks ( $\pm 1$  week) after discontinuation of investigational product, subjects will be contacted for a follow-up by telephone. They will be asked to return to clinic according to the 8 monthly visit schedule and in addition be contacted by telephone at a time corresponding to the 4-monthly visit they would have otherwise made to replenish study medication supply. If instead of these interim telephone contacts the subject prefers to attend clinic every 4 months as originally scheduled that is an acceptable alternative.

If a subject permanently discontinues investigational product and is unable to attend visits in-person, he/she will be contacted by telephone or other methods to assess study outcomes and vital status, unless the subject has specifically withdrawn consent for all forms of contact. Follow-up of subjects who withdraw consent for contact is described below.

Every effort should be made to educate the subjects on the importance of remaining in the study and attending scheduled study visits including those required after early discontinuation of investigational product.

Other subject follow-up options to collect study outcomes and vital status should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes and vital status is acceptable to the subject, then the subject will be deemed not to have withdrawn consent for follow-up.

##### **4.5.1. Withdrawal of Consent for Contact**

Subjects who no longer wish to attend study visits in-person will be asked to be contacted by telephone or other methods to assess study outcomes and vital status. However, if a subject specifically withdraws consent to be contacted for additional information, no further study visits or study-related telephone contacts can be conducted. Information regarding study outcomes or vital status will continue to be collected from available sources including those in the public domain. Additionally, alternative permitted options to obtain study outcomes and vital status will be reviewed based on accepted local laws and regulations. For any subject who withdraws consent for contact, the study site will be asked to document the discussion with the subject regarding each of the contact options that were offered.



#### **4.5.2. Subjects Deemed Lost to Follow-up**

Finally, investigators should make every effort to contact subjects who are deemed lost to follow-up and who have not withdrawn consent to follow-up contacts, including pursuing any alternative contact methods permitted by local regulations. Where permitted, a third party may be used to locate alternative subject contact information that will be provided to the investigator. All attempts to contact subjects will be documented in the subject's eCRF and source notes.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject. Should the subject continue to be unreachable, then and only then will he/she be considered "Lost to Follow-up". Nonetheless, efforts to attempt to locate and contact the subject will continue until the study end.

### **5. STUDY TREATMENTS**

#### **5.1. Investigational Product and Other Study Treatment**

Albiglutide (and albiglutide matching placebo) will be provided as a fixed-dose, fully disposable pen injector system for delivery of the investigational product (albiglutide or albiglutide matching placebo) from a prefilled dual chamber glass cartridge that is an integral part of the pen. The pen is intended for single use by the subject. It is designed for manual reconstitution of the dose, priming and insertion of the pen needle, and manual injection by the subject.

Albiglutide (or albiglutide matching placebo) is intended for self-administration as a subcutaneous injection in the abdomen, thigh or upper arm region. Rotation of use of injection sites is recommended. Albiglutide and insulin may be injected in the same body region but the injections should not be adjacent to each other. The albiglutide pen includes a mechanical locking system that prevents the user from manipulating the dose button before the cartridge has been fully reconstituted. Reconstitution is performed through rotation of the pen housing parts. The pen is designed to work with standard pen needles.

When the injector pen product is reconstituted by the subject, a neutral, isotonic solution is produced. Separate pens are required to deliver either 30 mg of albiglutide, 50 mg of albiglutide, or matching placebo in a 0.5-mL injection volume.

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

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS)

describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

The investigational product (albiglutide and albiglutide matching placebo) must be stored in a secure area at 2°C to 8°C and protected from freezing. Each site must maintain a temperature log. Access to and administration of the investigational product will be limited to the investigator and authorised site staff (investigator or designee). Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Procedures for the disposal of unused study treatment will be provided in the SRM.

Investigational product (albiglutide or albiglutide matching placebo) will be administered once weekly by subcutaneous injection. The first dose is to be administered at the clinic. The starting dose of albiglutide will be 30 mg once weekly. If at any stage after 5 weeks of treatment in the opinion of the investigator the subject needs to have intensified therapy to improve glycaemic control, the dose of investigational product should be increased before altering the doses of other glucose-lowering medication. In this case the subject will be called in for an unscheduled visit to supervise an increase in dose from 30 mg to 50 mg. Subjects randomly assigned to albiglutide matching placebo will also go through the increased dose procedure to maintain study blind. If a subject experiences tolerability issues with the higher, 50mg dose then the investigator may decrease the dose back to 30 mg without the need for an unscheduled visit to supervise down titration, other than for the subject to collect pens of the correct dose.

Albiglutide (or albiglutide matching placebo) may be administered at any time of day without regard to meals. Preferably, it should be administered once a week on the same day each week. The day of weekly administration can be changed if necessary as long as the last dose was administered 4 or more days previously. If a dose is missed, it should be administered as soon as possible within 3 days after the missed dose. Thereafter, subjects can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, subjects should wait and administer their next regularly scheduled weekly dose.

If a subject misses 4 or more consecutive doses, the investigator should contact the medical monitor to discuss options for helping assure better compliance.

## **5.2. Treatment Assignment**

Subjects will be assigned to study treatment in accordance with the randomisation schedule.

Randomised treatment assignment will be done via the Interactive Voice Response System (IVRS), and randomisation will be implemented based on a sequestered fixed randomisation schedule. Study centre personnel will call the IVRS once a subject has met all prerequisites for randomization; the IVRS will assign treatment.

Blinded study centre personnel will receive a randomisation notification indicating the unique subject identifier (randomisation number) and the date and time of randomisation. Each randomisation number will be a unique identifier. Once a randomisation number has been assigned, the number will not be reused even if the subject withdraws before receiving any investigational product. Details of the treatment assignment process are contained in the SRM.

### 5.3. Blinding

This is a double-blind study, neither the subject nor the study physician will know which of the two treatments (albiglutide or placebo) the subject is receiving.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency or in the event of a serious medical condition, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator**. Investigators have direct access to the subject's individual study treatment. It is preferred (but not mandatory) that the investigator first contacts the GSK Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment. If GSK study personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be fully documented in the appropriate data collection tool.

If a subject is unblinded by the investigator or treating physician then discontinuation of investigational product treatment for that subject will be at the discretion of the investigator. However, the subject should continue to be followed in the study (see Section 4.5).

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

### 5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned unused by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

### 5.5. Treatment Compliance

Subjects will be instructed to return all unused and used injector pens at the visits specified in the Time and Events Table (Table 1) in order to perform drug accountability

and determine compliance. Subjects will be provided with a sharps container for the disposal of used pens. To comply with health and safety considerations there will be no count made of used pens; only returned unused pens will be counted. In addition, subjects will be provided with a pre-printed card at each dispensing visit to record the date of each dose. The card is to be returned at the next dispensing visit with the unused pens.

## **5.6. Concomitant Medications and Non-Drug Therapies**

### **5.6.1. Permitted Medications and Non-Drug Therapies**

The usual care provider will manage the subjects according to standard of care, following local prescribing information. Close adherence to professional society guidelines for standard of care therapies in type 2 diabetes and cardiovascular disease will be emphasized during study conduct. Standard of care is described in greater detail in Section 3.2.

Unless specified as a prohibited medication in Section 5.6.2, all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned.

Like other members of the class, albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. This should be taken into account by investigators when prescribing concomitant medication.

It may be necessary to reduce the dose of concomitantly administered insulin secretagogues (such as SUs) or insulin to reduce the risk of hypoglycaemia when starting albiglutide.

All concomitant anti-hyperglycaemic medications (name of agent, total daily dose, start and stop dates) will be recorded in the eCRF at each visit. Concomitant cardiovascular medications taken during the study will also be recorded at each visit by class of agent. Additionally, all medications used within the 30 days prior to the onset and throughout the duration of an SAE, AE of special interest (Section 6.2.3), or an AE leading to discontinuation of investigational product will be recorded as individual agents, reason for use, together with start dates (and stop dates if applicable) and any changes since any previous AE.

### **5.6.2. Prohibited Medications and Non-Drug Therapies**

Subjects may not take a GLP-1 receptor agonist (other than blinded investigational product), nor any investigational drug, during the study (and any follow-up period after discontinuing investigational product).

If a subject receives a prohibited medication, a protocol deviation will be recorded.

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

Following the final study visit subjects will be contacted by telephone  $5 \pm 1$  weeks after last dose of study medication to assess any AEs ongoing since the last visit or newly emergent.

Subjects will be treated as deemed appropriate by the investigator following the end of the study. Investigational product will not be provided to subjects by GSK after the end of the study.

The half-life of albiglutide is approximately 5 days, and significant therapeutic concentrations can persist for 3 to 4 weeks after discontinuation. The choice of other medicinal products and dose selection should be considered accordingly, as adverse reactions may continue and efficacy may, at least partly, persist until albiglutide levels decline.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition whether or not GSK is providing specific post study treatment.

## **5.8. Treatment of Study Treatment Overdose**

No data are available with regard to albiglutide overdose in humans. The highest recommended dose of albiglutide is 50 mg once weekly.

During clinical studies of subjects with type 2 diabetes, the highest dose of albiglutide administered was 100 mg subcutaneously every four weeks for 12 weeks. This dose was associated with an increased frequency of nausea, vomiting, and headache.

There is no specific antidote for overdose with albiglutide. In the event of a suspected overdose, the appropriate supportive clinical care should be instituted, as dictated by the subject's clinical status. Anticipated symptoms of an overdose may be severe nausea, vomiting or headache. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the half-life of albiglutide (5 days).

## **6. STUDY ASSESSMENTS AND PROCEDURES**

The schedule of study assessments is shown in [Table 1](#) and [Table 2](#). Detailed procedures for each assessment are provided in the SRM.

**Table 1 Time and Events Table**

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post rand.)	Clinic Visit Month 4 ± 18 days then every 4 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Final study clinic visit <sup>4</sup> (or early withdrawal)	Follow up Phone Call 5 ± 1 weeks after last IP dose
Written informed consent	X						
Review of Inc/excl criteria	X	X					
Demography & directed medical history	X						
Assessment of MACE and micro-vascular events				X		X	
HbA1c	X <sup>5</sup>			X		X	
Serum creatinine (eGFR)	X <sup>5</sup>			X (alternate visits) <sup>2</sup>		X	
Liver Function Tests (LFTs) <sup>6</sup>		X		X (alternate visits) <sup>2</sup>		X	
Record available information on most recent lipid assessment <sup>7</sup>		X		X (annually)		X	
Genetic sampling <sup>8</sup>		X					
Patient reported outcomes questionnaires <sup>9</sup>		X <sup>10</sup>		X (alternate visits) <sup>2</sup>		X	
Key concomitant non-diabetes medication		X		X		X	X
Diabetes medication		X		X		X	X
Study drug reminder			X	X	X		
Physical examination <sup>11</sup>		X		X (alternate visits) <sup>2</sup>		X	
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X	X	X	X
Pregnancy test <sup>12</sup>	X	X					
Study drug dispense/compliance <sup>13</sup>		X		X	X	X	

1. Subjects who discontinue investigational product should be handled as described in Section 4.4 and Section 4.5 and in Table 2.

2. Assessments at month 8, 16, 24 etc. will include patient reported outcomes questionnaires, serum creatinine (eGFR), LFTs and physical examination. Those at months 4, 12, 20 etc do not.

3. Screening and Randomisation can occur at the same visit if all eligibility information is available. If Screening and Randomisation occur at the same visit assessments should not be duplicated.

4. Once it is projected that the target number of MACE events will have been collected and that the projected median duration of subject follow-up is at least 1.5 years, a 3 month window will be defined for conducting the final, face to face visit.

5. HbA1c and creatinine assessed using local laboratories at Screening visit and measured no more than 6 months prior to randomisation. If HbA1c or creatinine have not been assessed in the previous 6 months assessments to be performed via a central laboratory and results available prior to randomization. The investigator has the discretion to repeat

screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.

6. Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT. Blood samples for LFTs at randomization must be collected prior to the first dose of investigational product.
7. Lipid values (TC, LDLc, HDLc, Tg) to be recorded as available from routine clinical care at baseline and annually thereafter. If results are unavailable, lipids tests are not to be performed for the study.
8. Informed consent for genetic research must be obtained before collecting a sample. This can be collected at any time after genetic consent has been obtained and randomisation has occurred.
9. TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
10. TRIM-D is not required for subjects whose diabetes is treated by diet and exercise alone at Baseline.
11. See Section 6.2.7.
12. Only applies to women of child bearing potential. At screening perform urine pregnancy test. If positive, send serum sample to the central laboratory for confirmation. At Randomisation perform a urine pregnancy test. If result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised. If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. See Section 6.2.6.
13. Study drug dispensing not performed at final visit, compliance check not performed at Randomisation.

**Table 2 Time and Events Table for Subjects Who Permanently Discontinue IP Prior to the End of the Study**

Procedures	Clinic visit as soon after permanent discontinuation of IP as possible	Phone Call 5 ± 1 week after last IP dose	Continue contact schedule established at randomisation 4 monthly ± 1 month. <i>Telephone</i> <sup>1,2</sup>	Continue contact schedule established at randomisation 4 monthly ± 1 month. <i>Clinic visit</i> <sup>1,3</sup>	Final study clinic visit <sup>4</sup>
Assessment of MACE and micro-vascular events	X		X	X	X
HbA1c	X			X	X
Serum creatinine (eGFR)	X			X	X
Liver Function Tests (LFTs) <sup>5</sup>	X			X	X
Record available information on most recent lipid assessment <sup>6</sup>	X		X (annually)	X (annually)	X
Patient reported outcomes questionnaire <sup>7</sup>	X				
Key concomitant non-diabetes medication	X	X	X	X	X
Diabetes medication	X	X	X	X	X
Physical examination <sup>8</sup>	X			X	X
AEs leading to IP discontinuation	X				
SAEs, AEs of special interest,	X	X	X	X	X
Study drug compliance	X				

1. After subjects permanently discontinue IP, follow-up should continue on the 4-monthly schedule established at randomisation.
2. Where a subject would have been scheduled to attend clinic at months 4, 12, 20, 28 etc after randomisation, a telephone contact will be performed instead (with assessments as shown above).
3. Where a subject would have been scheduled to attend clinic at months 8, 16, 24, 32 etc after randomisation, a clinic visit will be performed (with assessments as shown above). If a subject who has permanently discontinued IP is unable to attend clinic then they will be contacted by telephone instead and the telephone contact assessments will be performed.
4. Once it is projected that the target number of MACE events will have been collected and that the projected median duration of subject follow-up is at least 1.5 years, a 3 month window will be defined for conducting the final, face to face visit.
5. Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT.
6. Lipid values (TC, LDLc, HDLc, Tg) to be recorded as available from routine clinical care annually. If results are unavailable, lipids tests are not to be performed for the study.
7. TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
8. See Section 6.2.7.



## 6.1. Critical Baseline Assessments

Disease, and therapy history, including cardiovascular medical history/risk factors will be assessed at Baseline. Investigators are encouraged to implement lifestyle modifications and adjust or initiate the appropriate pharmacotherapy throughout the study as recommended by current locally followed therapeutic cardiovascular and diabetes guidelines for participants in the study. Screening and randomisation can occur at the same visit depending on availability of information to determine eligibility of the subject to enter the study.

## 6.2. Safety

The following sections provide further detail on the safety assessments. Planned time points for all safety assessments are listed in the Time and Events Table ([Table 1](#)). Unscheduled visits will occur as medically necessary. Detailed procedures for obtaining each assessment are provided in the SRM.

Safety endpoints are described in [Section 2](#) and will include monitoring of cardiovascular events ([Section 6.2.1](#)), deaths, AEs of special interest ([Section 6.2.3](#)), clinically significant microvascular events ([Section 6.2.4](#)), SAEs and AEs leading to discontinuation of investigational product.

Liver chemistry stopping and follow-up criteria and AEs are described in [Section 4.4.3](#) and [Appendix 3](#).

### 6.2.1. Cardiovascular Events

Events referred to the CEC by the investigator as potential endpoints or transient ischemic attacks (TIAs) will not be collected or reported as SAEs, regardless of the adjudication outcome ([Section 6.2.2](#))<sup>1</sup>. These events will be reviewed by an Independent Data Monitoring Committee ([Section 9.8](#)).

The CEC will review and adjudicate the following clinical events:

Myocardial infarction

Stroke

Unstable angina requiring hospitalization

Hospitalization for heart failure

Sudden cardiac death

TIA

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<sup>1</sup> There is one exception to this statement. Per requirement of the Mexican Ministry of Health, all events referred to the CEC by Mexican investigators will also be submitted as SAEs to the Mexican Ministry of Health.

In addition, all clinical events submitted for adjudication and all other SAEs with a fatal outcome will be reviewed and adjudicated to classify the cause of death as cardiovascular or non-cardiovascular.

When the local investigator reported event and the CEC decision on the nature of the event differ, the CEC's decision will be considered final. The detailed descriptions of the endpoint (and TIA) definitions necessary for adjudication are contained within the CEC Charter (available on request). The guiding principle will be the "2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular and Stroke End Point Events for Clinical Trials" [ACC/AHA, 2014] and the "Third Universal Definition of Myocardial Infarction" endorsed by the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation (WHF) [Thygesen, 2012].

Source documentation required to support the adjudication of the events is described in the SRM. Recording of potential endpoint and TIA events in the eCRF and submission of source documentation will be required for clinical events meeting reporting criteria whether or not an endpoint event is suspected by the investigator.

#### **6.2.1.1. Other CV Events**

GSK has identified other CV events of special interest for all clinical studies. Investigators will be required to fill out event specific data collection tools for the following cardiovascular events which meet SAEs criteria or are non-serious events that result in discontinuation of investigational product:

Arrhythmias (other than atrial fibrillation/flutter, see Section 6.2.3)

Valvulopathy

Pulmonary hypertension

Peripheral arterial thromboembolism

Deep venous thrombosis/pulmonary embolism

Revascularisation (other than urgent revascularisation for unstable angina, a component of a secondary endpoint)

This information should be recorded in the specific cardiovascular eCRF within one week.

#### **6.2.2. Adverse Events (AE) and Serious Adverse Events (SAEs)**

The definitions of an AE or SAE can be found in [Appendix 5](#).

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

For this study events of myocardial infarction, stroke, unstable angina requiring urgent revascularization, hospitalization for heart failure, TIA and sudden cardiac death will not be collected or reported as AEs or SAEs. These events will be collected separately,

subjected to blinded adjudication by an independent CEC using prespecified diagnostic criteria, and reported separately (Section 6.2.1.1). All other events that meet serious criteria as defined in [Appendix 5](#) should be reported as SAEs.

All events with an outcome of death will be adjudicated to classify the cause of death as specifically cardiovascular or non-cardiovascular. Any event resulting in death should be reported as a SAE unless the event is myocardial infarction, stroke, unstable angina w/ urgent revascularization, Heart failure, TIA or sudden cardiac death which the protocol specifies are not to be collected as adverse events.

The study will not collect all non-serious AEs. Non-serious AEs leading to discontinuation of investigational product and non-serious AEs of special interest (see Section 6.2.3) will be collected.

Any events not specifically addressed above should be reported as an AE or SAE according to the definitions in [Appendix 5](#).

#### **6.2.2.1. Time period and Frequency for collecting AE and SAE information**

AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 6.2.2.3), at the timepoints specified in the Time and Events Table ([Table 1](#)).

Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.

Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

All SAEs will be recorded and reported to GSK within 24 hours, as indicated in [Appendix 5](#).

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

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in [Appendix 5](#).

#### **6.2.2.2. Method of Detecting AEs and SAEs**

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

“How are you feeling?”

“Have you had any (other) medical problems since your last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

Additionally subjects will be asked specific questions about the occurrence of AEs of special interest (Section 6.2.3).

#### **6.2.2.3. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 6.2.3) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 4.5). Further information on follow-up procedures is given in Appendix 5.

#### **6.2.2.4. Sentinel Events**

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

Acquired Long QT Syndrome

Agranulocytosis/severe neutropenia

Anaphylaxis and anaphylactoid reactions (see also Section 6.2.3)

Hepatotoxicity (see also Section 6.2.3)

Acute renal failure

Seizure

Stevens Johnson syndrome/toxic epidermal necrosis

#### **6.2.2.5. Regulatory Reporting Requirements for SAEs**

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

### **6.2.3. Adverse Events of Special Interest**

The investigator or site staff will be responsible for detecting, documenting and reporting events the following AEs of special interest:

Development of thyroid cancer

Haematologic malignancy

Pancreatic cancer

Pancreatitis

Injection site reactions

Immunological reactions (e.g., drug hypersensitivity reactions involving anaphylaxis/anaphylactoid reactions, acute bronchoconstriction, angioedema, and/or acute urticaria)

Severe hypoglycaemia events (which includes all events meeting the definition of SAEs [Appendix 5](#))

Hepatic events

Hepatic enzyme elevations (including GGT)

Serious GI events

Appendicitis

Atrial fibrillation/flutter

Pneumonia

Worsening renal function

Diabetic retinopathy

The results of any investigation should be recorded in the relevant sections of the subjects' eCRFs. In addition, for thyroid, pancreas or haematological malignancies a copy of the histopathology report and a discharge summary if the subject was admitted, or any available case summary (e.g. clinic letter), is to be provided to the Sponsor, if available.

Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. In subjects where a treatment emergent thyroid nodule is identified, if serum calcitonin is measured at the discretion of the Investigator (e.g., per local guidelines) and found to be >100 ng/L this should prompt further investigation for MTC and potential interruption or discontinuation of

investigational product until diagnosis has been resolved. If MTC or other thyroid C-cell neoplasia is diagnosed, albiglutide will be discontinued.

A Pancreatitis Adjudication Committee composed of independent specialists in gastroenterology will review all cases of possible pancreatitis.

Subjects should also be closely monitored for signs of potential allergic or drug hypersensitivity reactions including anaphylaxis, angioedema, generalized urticaria, and other potential manifestations of systemic allergic or drug hypersensitivity reactions. A serum sample should be taken as soon as possible after any such event in order to measure antibody to the drug. Instructions for sample processing are in the SRM. These events should be reported as AEs or SAEs based on the clinical evaluation of the subject. The reactions should be followed to completion as typical for any AE or SAE. Subjects with allergic or drug hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology should have investigational product withdrawn and not re-introduced.

Episodes of severe hypoglycaemia will be recorded according to subject report. Severe hypoglycaemic incidents will be defined as those episodes of hypoglycaemic symptoms for which the subject required assistance from another person and from which the subject recovered promptly after oral carbohydrate, intravenous glucose, glucagon administration or other resuscitative actions (definition per ADA Workgroup on Hypoglycaemia [Seaquist, 2013]). Additionally, all episodes of hypoglycaemic symptoms which in the investigator's opinion meet the definition of a SAE (defined in [Appendix 5](#)) will be included as severe hypoglycaemic episodes. During this study, if a subject's eGFR approaches 30mL/min/1.73m<sup>2</sup> closer monitoring of renal function is considered prudent, according to standard clinical practice. If eGFR is <15mL/min/1.73m<sup>2</sup> follow the procedure set out in Section [4.4.4](#).

#### **6.2.4. Clinically Important Microvascular Events**

Clinically important microvascular events are defined as the following: need for renal transplant or dialysis, new diabetes-related blindness, and procedures (laser photocoagulation or anti-vascular endothelial growth factor treatment or vitrectomy for diabetic retinopathy/eye disease). Clinically important microvascular events will be reported as recorded in the eCRF by the investigator without adjudication.

The AEs associated with the above outcomes or treatments should be reported separately as an AE or SAE according to the definitions in [Appendix 5](#).

#### **6.2.5. Pregnancy**

If a subject becomes pregnant during the study they should discontinue Investigational Product.

Details of all pregnancies in female subjects will be collected after the start of dosing and until the end of the Post-treatment Follow-up Period.

If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in [Appendix 6](#).

### 6.2.6. Clinical Laboratory Assessments

All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Table 1). Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all central laboratory safety parameters will be provided to the site.

If additional non-protocol specified laboratory assessments result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE of special interest or dose modification) the results must be recorded in the CRF.

Refer to the SRM/laboratory manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

The following laboratory assessments will be performed: serum creatinine, HbA1c, liver function tests [AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin, GGT], and urine and serum  $\beta$ hCG pregnancy test (for women of child bearing potential). All study-required laboratory assessments will be performed by a central laboratory, with the exception of HbA1c and creatinine at Screening and urine pregnancy test at Screening/Randomization.

#### Screening HbA1c and serum creatinine

Screening HbA1c and serum creatinine values should be based on the most recent local laboratory values taken as part of usual care within the previous 6 months and the values entered into the eCRF. These assessments must have been performed at an accredited laboratory. HbA1c screening results must be either Diabetes Control and Complications Trial (DCCT) aligned or International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardized. HbA1c screening results from point of care equipment are acceptable provided that the equipment is maintained by an accredited laboratory. If HbA1c or creatinine have not been assessed in the previous 6 months, laboratory assessments will be performed via the central laboratory to determine eligibility (if a local laboratory is used in error the results are acceptable for determining eligibility). The investigator has the discretion to repeat screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.

Re-screening of subjects who did not meet the eligibility criteria for HbA1c or creatinine based on local laboratory values taken as part of usual care is permitted. If values were based on laboratory results as part of usual care then one re-test is permitted within the protocol at Screening. Any future re-screening will be based on laboratory results obtained as part of usual care.



**Pregnancy testing (for women of childbearing potential)**

At the screening visit perform a urine pregnancy test. If the urine pregnancy test is positive, send a serum blood sample to the central laboratory for confirmation of pregnancy.

At the Randomisation visit perform a urine pregnancy test. If the result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised (provided all other eligibility criteria have been met).

If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. Do not randomise if the urine pregnancy test is positive; send a serum blood sample to the central laboratory for confirmation of pregnancy. If the urine pregnancy test is negative then the subject can be randomised at the same visit (provided all other eligibility criteria have been met).

**Lipids**

Where serum lipid tests have been performed as part of the subject's routine clinical care (i.e. not as a study procedure) the most recent results should be recorded at baseline and annually thereafter. The lipid parameters to be recorded are total cholesterol (TC), low density lipoprotein cholesterol (LDLc), high density lipoprotein (HDLc) and triglycerides (Tg).

If any or all of these results are not already available from the subject's records then separate lipid tests should not be performed solely for the study.

**6.2.6.1. Estimated Glomerular Filtration Rate (eGFR)**

Serum creatinine will be measured every 8 months by a central laboratory. It will be used to calculate eGFR using the MDRD formula [Levey, 2009], namely:

$$\text{eGFR (ml/min/1.73m}^2\text{)} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}).$$
**6.2.7. Physical examination**

A general physical examination, including height and neck (thyroid), will be performed at randomization. A targeted physical examination will be performed at all other time points as specified in the Time and Events Table (Table 1). The targeted physical examination will evaluate the cardiovascular system and injection sites and will include measurement of blood pressure and heart rate taken with the subject either in a semi-recumbent or seated position after at least a 5-minute rest period.



### **6.3. Value Evidence and Outcomes**

#### **6.3.1. Value Evidence and Outcomes Assessments**

##### **6.3.1.1. Treatment Related Impact Measure – Diabetes (TRIM-D)**

In order to evaluate satisfaction with treatment and to compare satisfaction across treatment groups, the TRIM-D questionnaire will be self administered by all subjects at baseline (except for subjects whose diabetes is treated by diet and exercise alone) and all subjects at each 8 month visit (and, to the extent possible, at the time of study completion or withdrawal from the study).

The TRIM-D, developed in 2009, is a 28-item treatment satisfaction measure scored to produce 5 sub-scale scores (Treatment Burden, Daily Life, Diabetes Management, Psychological Health, and Compliance) as well as a total score. It is available in a wide range of translations.

The TRIM-D development, in accordance with the principles of the Food and Drug Administration Patient Reported Outcome Guidance document, was based on findings from the published literature including content from already-existing treatment satisfaction measures as well as significant input from subjects with type 1 and with type 2 diabetes and from expert diabetes clinicians. The TRIM-D has been evaluated in a sample of 507 subjects (74% with type 2 diabetes) and has been shown to have acceptable reliability and validity [Brod, 2009a]. Its responsiveness was also evaluated in a sample of 242 subjects (71% with type 2 diabetes) and found to be acceptable [Brod, 2009b]. Some preliminary work has been done on estimating its minimal important difference but this needs further exploration [Brod, 2009b].

##### **6.3.1.2. EQ-5D**

The EQ-5D will be self-administered by subjects in order to measure generic health status. Combining the EQ-5D with the disease-specific TRIM-D, which is designed to have maximum sensitivity to relevant aspects of disease related treatment, will provide a more robust evaluation of the impact of treatments for type 2 diabetes and allow for clearer interpretation of study results. TRIM-D results, if consistent with the general trends seen in the EQ-5D, will have enhanced credibility.

The EQ-5D is a standardized instrument used to evaluate generic health-related quality of life. It is applicable to a wide range of health conditions and treatments, and it provides a simple descriptive profile and a single index value for health status. It is also used to provide utilities, or preference weights, for use in economic (cost effectiveness) evaluations. It is available in 141 self complete official language versions.

The EQ-5D has been used extensively in studies to measure the impact of type 2 diabetes and treatments for the disease. A systematic review identified 54 publications reporting EQ-5D responses and 39 papers presenting evidence on the measurement properties of the EQ-5D in this population [Janssen, 2011]. This evidence supported the validity, reliability, and responsiveness of the EQ-5D for evaluating health-related quality of life in subjects with type 2 diabetes. Other studies reported that index scores from the EQ-5D

have been shown to be an independent predictor of the risk of mortality, future vascular events, and other complications in people with type 2 diabetes [Clarke, 2009]. In addition, the SHIELD longitudinal study (1,741 respondents with type 2 diabetes and 4,543 without diabetes) used the EQ-5D to assess the 5-year changes in health-related quality of life in type 2 diabetes [Grandy, 2012].

#### **6.3.1.3. Exploratory Diabetes Management Questions**

In addition to the standardised instruments described above, patient experience in relation to the management of their diabetes will be evaluated in a subset of sites using a small number of self-administered diabetes management questions. These types of customized questions have been used successfully in asthma and in diabetes when patients are involved with goal-setting [Juniper, 1992; Anderson, 2010]. This tailored approach is an opportunity to capture data in the study that are not otherwise available from standard PRO measures such as the TRIM-D and the EQ-5D. As an exploratory endpoint, this set of questions (3 items at baseline, and at each 8 month follow-up visit) imposes very little patient or site burden, but can offer critical insight into the one area of the patient's choosing that s/he finds most difficult to manage. In addition, this patient-centred endpoint has the potential to be sensitive to changes over time.

These questions have been developed by GSK based on factors identified as important to subjects in the development of published, validated and reliable subject reported outcomes instruments in type 2 diabetes.

#### **6.3.1.4. Healthcare Resource Utilisation**

Data will be collected on the following healthcare resource use:

All cause hospitalisations and related healthcare resource use.

Healthcare resource use data will be collected in order to facilitate subsequent health-economic analyses comparing costs between albiglutide added to standard of care and placebo added to standard of care (cost is not an end point in the study).

Data on all-cause hospitalizations and related inpatient healthcare resource use will be collected. This will include:

All-Cause hospitalisation including: Admission and discharge diagnoses (primary and secondary), length of stay, level/type of ward, and time spent in Intensive Therapy Unit (or equivalent).

### **6.4. Genetic Research**

Information regarding genetic research is included in [Appendix 1](#).

## **7. DATA MANAGEMENT**

For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

## **8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS**

### **8.1. Hypotheses**

This trial will examine the following primary question:

- Whether albiglutide is non inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. Letting  $\lambda_1$  = hazard ratio for time to first MACE for albiglutide vs placebo, then:

Null hypothesis:  $\log \lambda_1 \geq \log(1.3)$

Alternative hypothesis:  $\log \lambda_1 < \log(1.3)$

- If non-inferiority is established, the effect on adjudicated MACE will be tested for superiority in a closed testing procedure. Letting  $\lambda_1$  = hazard ratio for time to first MACE for albiglutide vs placebo, then:

Null hypothesis:  $\log \lambda_1 \geq \log(1.0)$

Alternative hypothesis:  $\log \lambda_1 < \log(1.0)$

### **8.2. Study Design Considerations**

#### **8.2.1. Sample Size Assumptions**

The primary outcome will be analyzed such that the overall Type 1 error is no greater than 5% (two-sided). Specifically, the non-inferiority assessment of albiglutide compared to placebo will be conducted at 0.05 level, requiring one-sided significance at 0.025.

The power for MACE non-inferiority is calculated via the asymptotic variance and normality of the maximum likelihood estimator for the log-hazard ratio. Assuming a true hazard ratio of 1.0, 611 events will be needed to have 90% power to rule out non-inferiority margin of 1.3 for the hazard ratio with type I error of 0.05. A total of 9400 subjects will be enrolled and followed until it is projected that approximately 611 adjudicated MACE events will have occurred and the median duration of subject follow-

up is estimated to be at least 1.5 years. If, for example, the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years respectively, assuming that the number of subjects lost to follow-up accounts for 1% or less.

### 8.2.2. Sample Size Sensitivity for MACE non-inferiority

9400 subjects will be enrolled to cumulate the first MACE events experienced by 611 unique subjects. The study duration may vary depending on actual MACE event rate and duration of enrolment period. If the estimated median duration of subject follow-up is less than 1.5 years at the time that 611 events have occurred then study will continue until it is estimated that the median duration of subject follow-up is at least 1.5 years.

**Table 3 Indicative\* Total Study Duration Sensitivity for Varying MACE Event Rate and Duration of Recruitment**

MACE rate (% pa)	Duration of recruitment			
	1.5 yrs	2.0 yrs	2.5 yrs	3.0 yrs
2.0	4.1yrs	4.4yrs	4.6yrs	4.9yrs
2.5	3.4 yrs	3.7yrs	3.9yrs	4.2yrs
3.0	3.0yrs	3.2yrs	3.5yrs	3.8yrs
3.5	2.7yrs	2.9yrs	3.2yrs	3.4yrs

\* Although indicative, other scenarios are possible

### 8.2.3. Sample Size Re-estimation

The aggregate blinded event-rate data will be periodically reviewed by the Executive Committee and the sponsor. The study has an event-driven design and also requires that the projected median duration of subject follow up be at least 1.5 years. Should emerging data diverge significantly from protocol assumptions, the total sample size and/or follow up time may be adjusted, within the bounds of feasibility, to achieve the event target.

## 8.3. Data Analysis Considerations

### 8.3.1. Analysis Populations

The intent-to-treat (ITT) population will include all randomly assigned subjects. The ITT subjects will be analyzed according to randomised treatment. The inference for primary objectives in the study will be made from ITT population.

Per-protocol Population (PP) will exclude the subjects who have major protocol violations. Per-protocol analysis will include Per-protocol population only and their data upon to the time of discontinuation of investigational product plus 56 days.

The non-insulin population (NI) will include all subjects in the ITT population who are not on insulin at baseline. Inference for the time to insulin endpoint will be made from the NI population.

The baseline basal insulin user population (BI) will include all subjects in the ITT population who are on basal insulin, but not on other insulin at baseline. Inference for the time to prandial insulin endpoint will be made on BI population.

The safety population will include all enrolled subjects who receive at least 1 dose of study treatment. The safety population subjects will be analyzed according to the treatment received. The safety population will be used for analyses of safety objectives.

Other analysis populations will be defined in the RAP.

### **8.3.2. Analysis Data Set**

For time to event data, censoring time for subjects who lost to follow-up is defined as following:

For primary analysis, subjects who are lost to follow-up will be censored at the date of last evidence of confirmatory status for MACE events.

For on-treatment analysis, censoring date will be the last dose date.

For on-therapy analysis (on-treatment+56 days), censoring date will be the last dose date+56 days.

For analysis of all cause of mortality, censoring date will be the latest date known alive.

### **8.3.3. Treatment Comparisons**

Demographic and baseline characteristics (e.g., gender, age, racial or ethnic origin, height and weight, body mass index (BMI), blood pressure and other characteristics) will be summarized for each treatment group. In addition, smoking and alcohol habits, diabetic and cardiovascular medical history, baseline laboratory results, and prior medications will be summarized by treatment group. Binary and ordinal characteristics will be summarized by counts and percentages, while continuous variables will be represented by mean and standard deviations or medians and percentiles, as appropriate. Any variables with treatment imbalances may be considered as covariates for further analysis of an exploratory nature. Such covariates will be identified on the basis of the clinical relevance of the observed treatment difference.

#### **8.3.3.1. Primary Comparisons of Interest**

The primary endpoint will be the time to the first occurrence of MACE over the full duration of the study. A p-value for non-inferiority of the primary endpoint will be calculated from a Cox Proportional Hazards (PH) regression model with treatment group as the only covariate for the hypotheses described in Section 8.1. If non-inferiority is established, a p-value for superiority for the primary endpoint will be calculated from a Cox Proportional Hazards (PH) regression model with treatment group as the only covariate for the hypotheses described in Section 8.1.

### 8.3.3.2. Other Comparisons of Interest

For other analyses incidence rates will be presented for binary data and summary statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous data. Time to event endpoints will be evaluated via the p-value from a Cox PH regression model with treatment as the only covariate. Furthermore, summary statistics of change from baseline for HbA1c will be presented along with percent of subjects within ranges of clinical interest (e.g., HbA1c < 7.0%). Available lipid data will be summarized for descriptive purposes.

### 8.3.4. Interim Analysis

An IDMC will monitor progress of the study and ensure that it meets the highest standards of ethics and subject safety. All cardiovascular event data, together with other safety data, will be sent to the IDMC for review at approximately every 6 months after the first subject has been randomised to receive treatment. This frequency may be adjusted, if deemed necessary by the IDMC, depending on the enrolment rates and the rate of safety events. There are no plans to stop the study early for a non-inferiority or benefit claim, however should the IDMC identify in the course of its scheduled reviews overwhelming evidence of MACE benefit (e.g.,  $p < 0.001$ ), with directionally consistent findings on all-cause mortality, the IDMC might consider recommending early stopping. This approach essentially preserves the final alpha for the end-of-study analysis at 5% and hence there are no plans to adjust the final alpha on account on safety reviews conducted by the IDMC. The IDMC charter, reporting and procedures are outlined in separate documents.

### 8.3.5. Multiplicity Controls

If non-inferiority is established for the primary endpoint, the data will be used to test for evidence of superiority. This approach is a closed testing procedure, and therefore, no adjustment for multiplicity is required [Hung, 2009].

#### *Other Secondary Endpoints and Subgroup Analysis*

The following secondary endpoints will provide supportive evidence for cardiovascular safety and metabolic efficacy and will not use any multiplicity adjustment procedure. Results will be presented with confidence interval and nominal p-values:

Components of primary endpoint (MACE = cardiovascular death, MI, stroke)

MACE + urgent revascularisation for unstable angina

Cardiovascular death or hospitalisation for heart failure

Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start

Time to initiation of prandial insulin in those subjects treated with basal insulin at study start.

The proportion of subjects achieving glycaemic control ( $\text{HbA1c} \leq 7.0\%$  at final assessment) with no severe hypoglycaemic incidents and weight gain  $<5\%$  of body weight

Mean HbA1c at scheduled visits and change from baseline

Mean body weight at scheduled visits and change from baseline

Mean eGFR at scheduled visits and change from baseline

Composite microvascular endpoint

To examine the degree of consistency of the overall treatment effect in terms of important prognostic factors, subgroup analyses of the primary outcomes will be performed based on subject demographics and baseline characteristics. These exploratory subgroup analyses will not be adjusted for multiple comparisons and will be interpreted descriptively.

### **8.3.6. Key Elements of Analysis Plan**

Any deviations from the original analysis planned in the protocol agreed upon prior to finalization of the RAP, will be described in that document. Any additional changes to the planned analysis in the RAP will be described in the final clinical study report.

#### **8.3.6.1. Primary Analysis**

The primary analysis is an ITT analysis of the time to the first occurrence of MACE over the full duration of the study. Time to event analyses will be performed using Cox's Proportional Hazard regression with SAS PHREG with treatment group as the only covariate. Data for subjects without a primary event will be censored.

Treatment differences will be estimated via the hazard ratio and its 95% confidence interval (CI).

The hypothesis of non-inferiority of albiglutide relative to placebo group with hazard ratio less than 1.3 with respect to cardiovascular risk will be tested at the end of the study. If non-inferiority is established, the hypothesis of superiority of albiglutide relative to placebo will be tested.

The absolute risk difference per 100 PY, with its associated 95% confidence interval, will also be presented.

The product-limit estimates of the probabilities (and their standard errors) of first MACE over time will be computed and displayed as Kaplan-Meier (KM) survival curves for albiglutide and placebo groups. The KM curves will also be presented corresponding to the above comparisons.

The total number of all MACE or any of its components will be analyzed by Poisson regression model. The incidence rate per 100 person-years, relative risk and their 95% CI will be presented. Number of subjects who experienced at least one event, 2 or 3 or more MACE or its components will also be summarized by treatment group.

As sensitivity analyses, the analyses described above will be repeated using events occur while on-treatment and events occur during the period of on-treatment plus 56 days post last dose.

### **8.3.6.2. Secondary Endpoint Analysis**

Endpoints that supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes endpoints:

Supportive endpoints including the time to first occurrence of adjudicated MACE or urgent revascularisation for unstable angina, time to first occurrence of individual components of MACE, time to first occurrence of cardiovascular death or hospitalisation for heart failure will be analyzed using a proportional Cox regression model similarly as the primary endpoint.

Endpoints that evaluate the effects of albiglutide on metabolic management of type 2 diabetes:

Among the subjects who are not on insulin at baseline (NI population), time to insulin will be analyzed using a proportional Cox regression model similar to the primary MACE analysis. The product-limit estimates of the probabilities (and their standard errors) of adding insulin over time will be computed and displayed as Kaplan-Meier (KM) survival curves for albiglutide and placebo treatment groups. The KM curves will also be presented corresponding to the above comparisons.

The composite of the proportion of those achieving good control ( $HbA1c \leq 7.0\%$ ) AND having no severe hypoglycaemic incidents AND weight gain  $<5\%$  at the end of the study will be evaluated utilize nonparametric, covariance-adjusted, extended Mantel-Haenszel tests. Additional analysis will be provided for scheduled visits. Nominal p-values and 95% CIs will be presented for these visits. Time to introduction of prandial insulin in those on basal insulin  $\pm$  orals anti-hyperglycemic drugs at baseline will be analyzed using a Cox PH model and KM method similar to the primary endpoint.

Composite of microvascular events will be analyzed using a proportional Cox regression model and KM method similar to the primary endpoint.

HbA1c, body weight and eGFR will be analyzed using a repeated mixed effect model. The least square means, 95%CIs and nominal p-values will be presented.

Additional analysis will be performed to assess the incidence rate of recurrent severe hypoglycaemic events between treatment groups during the course of the study. A repeated Poisson regression model including treatment and visit as factors will be used to test treatment difference with offset for person years. An unstructured working correlation matrix will be used in the iterative estimation process. The model-adjusted least square incidence rate for each treatment as well as the treatment difference of the incidence rate will be reported. Events of severe hypoglycaemia will also be summarized descriptively by treatment group. Additional summary by baseline HbA1c, renal status and age subgroup will also be provided.

Further analysis details will be provided in the RAP.



### **8.3.6.3. Subgroup Analysis**

Separate subgroup analyses of the primary outcomes will be performed based on subject demographics and baseline characteristics. Subgroups may include sex, age group, BMI, whether subjects have history of a previous cardiovascular event, and baseline HbA1C, background of anti-hyperglycaemia treatment etc. The detail of subgroups will be pre-specified in the RAP. Consistency of treatment effects will be assessed using Cox regression, along with the 95% confidence intervals for the relative risk or hazard ratios for each subgroup a nominal alpha level for interaction of 0.10 will be used. The effect of treatment interaction with subgroups will also explored; however as the number of these subgroup variables may be large, the probability of observing at least one statistically significant result may be high. Thus these additional analyses will be considered exploratory regardless of the p-value associated with any interaction.

Further details will be provided in the RAP.

### **8.3.6.4. Other Safety Analyses**

Subject demographics, medical history, prior and concomitant medications, vital sign measurements, laboratory values, physical examination assessments, will be summarized by treatment group using descriptive statistics.

For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages.

For SAEs, AEs leading to permanent IP withdrawal and AEs of special interest, the number and percentage of subjects, total number of events and incidence density will be presented by treatment group and overall at the SOC and Preferred Term (PT) level. Relative Risk and its 95% CI may also be presented on a targeted basis. The time to first occurrence of specific events will be summarized.

All cause mortality will be summarized by treatment group and analyzed using a Cox PH model similarly as the-primary endpoint.

All events sent to CEC (including TIAs) will be summarized.

Pancreatitis events will be adjudicated by the independent Pancreatitis Adjudication Committee. The information for investigator reported pancreatitis events and its adjudication results will be summarized.

Further analysis details will be provided in the RAP.

### **8.3.6.5. Value Evidence and Outcomes Analyses**

TRIM-D total score and score for each domain will be summarized descriptively by treatment group and scheduled visit. Score changes from baseline will be compared between treatments for each visit by an ANCOVA model.

For EQ-5D, subjects' responses at each visit for the 5 domains will be summarized categorically by treatment group, together with the summary of utility score at each visit and change from baseline by treatment group. Change from baseline will be compared between treatment groups for each visit by an ANCOVA model.

For study specific PRO questions, responses will be summarized descriptively by treatment group and scheduled visit.

Healthcare resource use will be summarized by treatment group and visit.

Further analysis details will be provided in the RAP.

## **9. STUDY CONDUCT CONSIDERATIONS**

### **9.1. Posting of Information on Publicly Available Clinical Trial Registers**

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

### **9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process**

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

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH E6 Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

IRB/IEC review and favourable opinion/approval of the study protocol and amendments as applicable

Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)

Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Signed informed consent must be obtained for each subject prior to participation in the study

The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research. Optional assessments (including those in a separate protocol and/or under separate informed consent) and the

clinical protocol should be concurrently submitted for approval unless regulation requires separate submission. Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

### **9.3. Quality Control (Study Monitoring)**

In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study to ensure that the:

Data are authentic, accurate, and complete.

Safety and rights of subjects are being protected.

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

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

### **9.4. Quality Assurance**

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

### **9.5. Study and Site Closure**

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

GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

## **9.6. Records Retention**

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

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

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

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

## **9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication**

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

opportunity to review the complete study results at 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 subjects, as appropriate.

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

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.

### **9.8. Independent Data Monitoring Committee (IDMC)**

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter.

### **9.9. Pancreatitis Adjudication Committee**

Detailed information on suspected pancreatitis events will be collected on special pages of the eCRF. A Pancreatitis Adjudication Committee composed of independent specialists in gastroenterology will review cases of possible pancreatitis. Details of this committee and case adjudication are described in the committee's charter available on request.

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## 11. APPENDICES

### 11.1. Appendix 1: Genetic Research

#### Background

Genetics is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of genetic associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	<i>HLA-B*57:01</i> (Human Leukocyte Antigen B)	Carriage of the <i>HLA-B*57:01</i> variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective <i>HLA-B*57:01</i> screening and exclusion of <i>HLA-B*57:01</i> positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labelling in the United States and Europe now recommend (US) or require (EU) prospective <i>HLA-B*57:01</i> screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. <i>HLA-B*57:01</i> screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	<i>HLA-B*15:02</i>	Independent studies indicated that patients of East Asian ancestry who carry <i>HLA-B*15:02</i> are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of <i>HLA-B*15:02</i> prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	<i>UGT1A1</i> *28	Variations in the <i>UGT1A1</i> gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular <i>UGT1A1</i> gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the <i>UGT1A1</i> *28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful genetic research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable genetic analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to albigitide.

### Genetic Research Objectives

The objective of genetic research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to albigitide. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with albigitide, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

Safety and/or tolerability

Efficacy

### Study Population

Any subject who is enrolled in the clinical study, can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from genetic research.

Subject participation in the genetic research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

## Study Assessments and Procedures

Blood samples can be taken for deoxyribonucleic acid (DNA) extraction and used in genetic assessments.

If taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (~6ml) will be collected for the genetic research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomised and provided informed consent for genetic research, but may be taken at any time while the subject is participating in the clinical study.

The genetic sample is labelled (or “coded”) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilise the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct genetic analysis may be identified after a study (or a set of studies) of albiglutide has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to albiglutide.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

## Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

Continue to participate in genetic research with the genetic sample retained for analysis

Withdraw from genetic research and destroy the genetic sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time

when a subject wishes to withdraw from genetic research or have their sample destroyed whether during the study or during the retention period following close of the main study.

### **Screen and Baseline Failures**

If a blood sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

### **Analyses**

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to albiglutide. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and genetic research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of genetic investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

### **Informed Consent**

Subjects who do not wish to participate in genetic research may still participate in the clinical study. Genetic informed consent must be obtained prior to any blood being taken for genetic research.

### **Provision of Study Results and Confidentiality of Subject's Genetic Data**

GSK may summarise the genetic research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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## 11.2. Appendix 2: GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

1. Contraceptive subdermal implant that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label.
2. Intrauterine device or intrauterine system that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Trussell, 2011]
3. Oral Contraceptive, either combined or progestogen alone [Trussell, 2011]
4. Injectable progestogen [Trussell, 2011]
5. Contraceptive vaginal ring [Trussell, 2011]
6. Percutaneous contraceptive patches [Trussell, 2011]
7. Male partner sterilization prior to the **female subject's entry** into the study, and this male is the sole partner for that subject. The information on the male sterility can come from interview with the subject on her male partner's medical history.
8. Male condom **combined with a female** diaphragm, with or without a vaginal spermicide (foam, gel, film, cream, or suppository). In the UK it is a country-specific requirement of the regulatory authority (Medicines and Healthcare Products Regulatory Agency) that a vaginal spermicide be used.

These allowed methods of contraception have a failure rate of less than 1% per year but are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

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### 11.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

**Phase III-IV liver chemistry stopping and increased monitoring criteria** have been designed to assure subject safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).

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

#### Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
<b>ALT-absolute</b>	ALT $\geq$ 8xULN
<b>ALT Increase</b>	ALT $\geq$ 5xULN but <8xULN persists for $\geq$ 2 weeks ALT $\geq$ 3xULN but <5xULN persists for $\geq$ 4 weeks
<b>Bilirubin<sup>1,2</sup></b>	ALT $\geq$ 3xULN <b>and</b> bilirubin $\geq$ 2xULN (>35% direct bilirubin)
<b>INR<sup>2</sup></b>	ALT $\geq$ 3xULN <b>and</b> INR>1.5, if INR measured
<b>Cannot Monitor</b>	ALT $\geq$ 5xULN but <8xULN and cannot be monitored weekly for $\geq$ 2 weeks ALT $\geq$ 3xULN but <5xULN and cannot be monitored weekly for $\geq$ 4 weeks
<b>Symptomatic<sup>3</sup></b>	ALT $\geq$ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> <li>Immediately discontinue study treatment</li> <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 subject until liver chemistries resolve, stabilize, or return to within baseline (see <b>MONITORING</b> below)</li> <li><b>Do not restart</b> subject with study treatment unless allowed per protocol and GSK Medical Governance approval <b>is granted</b> (refer to</li> </ul>	<ul style="list-style-type: none"> <li>Viral hepatitis serology<sup>4</sup></li> <li>Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody<sup>5</sup>.</li> <li>Blood sample for pharmacokinetic (PK) analysis, obtained within 3 half lives (15 days) of last dose<sup>6</sup></li> <li>Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</li> <li>Fractionate bilirubin, if total bilirubin <math>\geq</math> 2xULN.</li> </ul>

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<p><a href="#">Appendix 5)</a></p> <ul style="list-style-type: none"> <li>• <b>If restart is not granted</b>, permanently discontinue study treatment and continue subject in the study for any protocol specified follow up assessments</li> <li>• Re-challenge is not allowed.</li> </ul> <p><b>MONITORING:</b></p> <p><b><u>For bilirubin or INR criteria:</u></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 hrs</b></li> <li>• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline</li> <li>• A specialist or hepatology consultation is recommended</li> </ul> <p><b><u>For All other criteria:</u></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> </ul> <p>Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline</p>	<ul style="list-style-type: none"> <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, other over the counter medications.</li> <li>• Record alcohol use on the liver event alcohol intake case report form</li> </ul> <p><b><u>For bilirubin or INR criteria:</u></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 pressure liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [<a href="#">James, 2009</a>]). <b>NOTE: not required in China</b></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 subject if ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN (>35% direct bilirubin) or ALT  $\geq$  3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants



3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

### Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
<p>ALT <math>\geq</math>5xULN and <math>&lt;</math>8xULN and bilirubin <math>&lt;</math>2xULN <b>without</b> symptoms believed to be related to liver injury or hypersensitivity, <b>and</b> who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT <math>\geq</math>3xULN and <math>&lt;</math>5xULN and bilirubin <math>&lt;</math>2xULN <b>without</b> symptoms believed to be related to liver injury or hypersensitivity, <b>and</b> who can be monitored weekly for 4 weeks.</p>	<ul style="list-style-type: none"> <li>• Notify the GSK medical monitor <b>within 24 hours</b> of learning of the abnormality to discuss subject safety.</li> <li>• Subject can continue study treatment</li> <li>• Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline</li> <li>• If at any time subject meets the liver chemistry stopping criteria, proceed as described above</li> <li>• If ALT decreases from ALT <math>\geq</math>5xULN and <math>&lt;</math>8xULN to <math>\geq</math>3xULN but <math>&lt;</math>5xULN, continue to monitor liver chemistries weekly.</li> <li>• If, after 4 weeks of monitoring, ALT <math>&lt;</math>3xULN and bilirubin <math>&lt;</math>2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.</li> </ul>

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Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol.* 2005;43(5):2363–2369.

## 11.4. Appendix 4: Liver Safety Drug Restart Guidelines

If subject meets liver chemistry stopping criteria do not restart subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the subject

If GSK Medical Governance approval to restart the subject with study treatment **is not granted**, then the subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

### ***Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment***

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).

Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury) or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.

Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.

If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.

The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.

Study treatment must be administered at the dose specified by GSK.

Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.

GSK to be notified of any adverse events, as per Section [6.2.2](#) and [Appendix 5](#)

## **11.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events**

### **11.5.1. Definition of Adverse Events**

<b>Adverse Event Definition:</b>
<p>An AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p> <p>NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.</p>

<b>Events <u>meeting</u> AE definition include:</b>
<p>Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.</p> <p>Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</p> <p>New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.</p> <p>Signs, symptoms, or the clinical sequelae of a suspected interaction.</p> <p>Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).</p> <p>The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.</p>

**Events NOT meeting definition of an AE include:**

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

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.

Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

**11.5.2. Definition of Serious Adverse Events**

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, etc).

**Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:**

**a. Results in death****b. Is life-threatening**

NOTE:

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

**c. Requires hospitalization or prolongation of existing hospitalization**

NOTE:

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

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

**d. Results in disability/incapacity**

## NOTE:

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

**e. Is a congenital anomaly/birth defect****f. Other situations:**

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

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

ALT  $\geq$  3xULN and total bilirubin\*  $\geq$  2xULN (>35% direct), **or**

ALT  $\geq$  3xULN and INR\*\*  $>$  1.5.

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

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

### 11.5.3. Recording of AEs and SAEs

#### **AEs and SAE Recording:**

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.

The investigator will then record all relevant information regarding an AE/SAE in the CRF

It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.

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

Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.

Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.

The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.



#### 11.5.4. Evaluating AEs and SAEs

##### Assessment of Intensity

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

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

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

Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

##### Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.

A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.

The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

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

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**

The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.

The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.

If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

**11.5.5. Reporting of SAEs to GSK****SAE reporting to GSK via electronic data collection tool**

Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool

If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the safety designee as detailed in the Study Reference Manual

The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.

Site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data

If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone.

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

## **11.6. Appendix 6: Collection of Pregnancy Information**

Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study

Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.

Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, 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 5](#). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

### **Any female subject who becomes pregnant while participating**

will discontinue study medication

## **11.7. Appendix 7: Electronic Health Record Ancillary Study**

### **11.7.1. Introduction**

#### **11.7.1.1. Background**

Clinical researchers and policy makers want to move towards embedding clinical trials directly within health care delivery systems in order to increase the relevance, speed, and efficiency of clinical research [Richesson, 2013]. The assumption is that the capabilities offered by Electronic Health Records (EHRs), along with concurrent changes in health care organization and delivery, and the development of a learning health system will transform the way clinical research is conducted [Etheredge, 2007; Greene, 2012].

In 2011, the National Heart, Lung, and Blood Institute (NHLBI) convened the NHLBI Working Group on Electronic Health Records: Research Priorities to Improve Cardiopulmonary Health in Clinical Practice. As part of their mission, this working group identified key research, policy, and training priorities [Curtis, 2014]. A key research priority was to leverage EHR tools to facilitate the efficient implementation of randomized clinical trials. Specific areas highlighted for increased efficiency included efficient data collection and outcome surveillance and confirmation.

#### **11.7.1.2. Literature Review**

Electronic Health Records were primarily designed to document patient care and facilitate billing and reimbursement. The large amount of electronic data that are captured may also facilitate clinical research and public health surveillance. EHR data are inherently complex, originate from various settings (e.g., outpatient practices, hospitals, and laboratories) and may be inconsistently captured across systems. Despite the complexity of EHR data, national networks have begun to use these data to improve public health and generate real-world evidence [Toh, 2012]. The Patient Centered Outcomes Research network (PCORnet) (pcornet.org) is a research network that is currently being designed to support observational comparative effectiveness research and clinical trials that are embedded in clinical care settings [Fleurence, 2014]. Similarly, the NIH Health Care Systems Research Collaboratory (nihcollaboratory.org) is creating infrastructure to improve the conduct of embedded clinical trials. One ongoing NIH Collaboratory trial is the Time to Reduce Mortality in End-Stage Renal Disease study (TiME) (clinicaltrials.gov identifier: NCT02019225). TiME will examine optimal hemodialysis session length using data from EHR systems through a partnership between academic investigators and two health care provider organizations with different electronic data systems. There are several other recent examples of clinical trials that were embedded in health care delivery systems [Gulliford, 2014; van Staa, 2014]. For instance, one recent study evaluated the use of an electronic decision support tool to improve risk factor control (i.e., blood pressure and cholesterol) following a cerebrovascular event with outcome data collected from the EHR [Dregan, 2014]. While the specific intervention was not shown to be efficacious, data acquisition via EHR sources was robust and implemented at a low cost.

### 11.7.1.3. Ancillary Study Rationale

Despite these earlier studies demonstrating the potential opportunities with EHR-based data acquisition, our understanding of how EHR-based platforms might increase the efficiency of data collection, outcome surveillance, and confirmation in an integrated manner is unknown. EHRs are inherently heterogeneous, with each implementation different from the next. The barriers to using EHR-generated lists of patients to facilitate trial enrolment, the fitness of EHR data for populating baseline characteristics in an electronic case report form (eCRF) and the use of EHR data to find events of interest during trial follow-up are not well characterized.

EHR systems contain a wealth of clinical data about patients who are connected to the health care delivery system and may be eligible for enrollment in a clinical trial. Anecdotal reports suggest that identification of potential patients using the EHR increases the number of patients to be screened but may not consistently translate to an increased number of patients enrolled. Causes are likely multi-factorial and may include the translatability of inclusion and exclusion criteria to structured clinical data and the algorithm used to identify potential patients. There is a need to empirically assess the utility of using an EHR-generated list of patients to facilitate trial enrolment as well as understanding the barriers to use of an EHR system for enrolment.

Structured data captured in the EHR may be similar to data elements specified in baseline patient characteristics in the eCRF, yet EHR data are collected primarily to support clinical care and reimbursement needs. Their fitness for use as source data for selected data elements of the baseline patient characteristics in the eCRF has not been established.

During routine trial follow-up, study coordinators typically gather information from various sources including direct patient contact and medical records (some of which resides in electronic format, i.e., an EHR) of the enrolling institution and outside facilities to document events for study participants. There is a need to specifically assess the utility of EHR data acquisition for follow-up events across multiple health systems, and to address challenges to the future use of EHR as source data for global trials and observational studies.

In summary, the EHR is a rich source of clinical data that are increasingly used in pragmatic health research initiatives, but the assumption that EHR data are fit for use in high-quality clinical research has not been rigorously evaluated. To provide evidence to address this knowledge gap, GlaxoSmithKline (GSK) and Duke Clinical Research Institute (DCRI) are committed to conducting an exploratory EHR Ancillary Study alongside a large pragmatic clinical trial. The overarching goal is to further our understanding of how EHR data can be organized into a query-able format to facilitate a more efficient, reliable, and cost-effective research process. As a collaboration between an academic research institute and a pharmaceutical sponsor, this project provides a unique opportunity to compare electronic health record data with baseline characteristics and adjudicated events captured as part of a large, contemporary, outcomes-based trial.

## **11.7.2. Ancillary Study OBJECTIVES**

### **11.7.2.1. Primary Objectives**

#### **Objective 1: Understand how EHR data are used to facilitate trial recruitment and the barriers to that use..**

Using site study coordinator surveys, workflow assessment, qualitative analysis of a site-level enrollment measure, and quantitative comparisons of enrolled patients with potentially eligible patients, this objective will enhance understanding of how EHR data are used to facilitate clinical trial enrollment at global HARMONY sites with an EHR system and who express interest in participating. All global sites with an EHR will be invited to participate in the qualitative component – which will occur after main study enrollment is complete. For select sites in the United States, a quantitative analysis will be conducted comparing the proportion of eligible patients identified by a computerized algorithm to the site's list of enrolled patients. Algorithms will be developed based on structured data that represent trial inclusion criteria and submitted as a query to a subset of select sites with EHR systems that meet certain criteria and have technical capabilities.

#### **Objective 2: Evaluate the fitness of EHR data for use in populating the baseline characteristics in the eCRF**

For select sites, the level of agreement between data extracted from the EHR and data documented on the baseline eCRF (reference standard) will be evaluated and compared among consented participants. This will occur after study completion and within selected data areas (e.g., demographics, medical history, concomitant medications). Additionally the performance of algorithms developed to identify comorbidities and other clinical concepts will be assessed at the site level and aggregated, where appropriate.

Other partnerships in select countries will support comparisons between data extracted from existing national-level electronic health data (or administrative claims data) and data documented on the baseline eCRF.

#### **Objective 3: Explore the use of EHR data to find events of interest during trial follow-up**

For select sites, case-finding algorithms will be developed for select specified endpoints (e.g., all-cause death, myocardial infarction, stroke, urgent revascularization for unstable angina, hospitalization for heart failure) and applied to EHR data. At the conclusion of the main HARMONY-Outcomes study, the performance of EHR algorithms will be compared with eCRF-reported and adjudicated eCRF-reported events (reference standard).

Other partnerships in select countries will support comparisons between data extracted from existing national-level electronic health data (or administrative claims data) and eCRF reported and adjudicated eCRF-reported events.

### **11.7.3. Ancillary Study design**

#### **11.7.3.1. Study Design**

The ancillary study will be conducted in conjunction with the HARMONY-Outcomes trial, a randomised, double blind, parallel-group, placebo-masked, controlled study to evaluate the effect of albiglutide on cardiovascular events in patients with Type 2 diabetes. Albiglutide will be administered subcutaneously once weekly in a population of patients with Type 2 diabetes and a previous history of cardiovascular disease and who do not have optimal glycaemic control. The majority of research activities in the ancillary study will take place following the close of the HARMONY Outcomes Trial, with specified timelines laid out in objective-specific workplans. Data extracted from the EHR for the purpose of the ancillary study will cover the time period from randomization into the main HARMONY Outcomes Trial study through the end of that study. Objective 1 will include a qualitative survey for which all global sites with an EHR who express interest in participating will be invited to participate. In select sites, Objective 1 will also include the application of a screening algorithm to support the quantitative aspect of the analysis. For Objectives 2 and 3, select U.S. sites with specific technical capabilities will participate, as well as select countries where relevant national-level electronic health data are available and accessible.

#### **11.7.3.2. Data Flow Strategies – Introduction**

The HARMONY EHR ancillary study will utilize two data flows, termed the DataMart and National strategies, to gather and analyze data. The DataMart strategy will support work done at select U.S. sites, in order to access electronic health record data from patients enrolled in the main HARMONY Outcomes trial at these sites. This strategy encompasses the quantitative section of Objective 1, as well as the entirety of Objectives 2 and 3. The National Strategy will support work done with global national partners, in order to access national electronic health data for patients enrolled in the main HARMONY Outcomes trial. This strategy will encompass only Objectives 2 and 3. More detailed information regarding these strategies can be found below in Section [11.7.3.4](#).

**11.7.3.3. Site Selection****Table 4 HARMONY Outcomes Site and Country Participation by Ancillary Study Objective**

Objective	Sites			Select Countries
	Selected U.S. Sites with Technical Capabilities* (DataMart Strategy)	Global Sites with an Implemented EHR System	U.S. VA Sites	U.S.** and Global Partners*** (National Strategy)
1: Qualitative	X	X		
1: Quantitative	X		X	
2	X		X	X
3	X		X	X

\*Technical capabilities include ability to extract data from the EHR and transform to a common data format

\*\*The U.S. National Strategy will acquire Medicare Claims data for Medicare beneficiaries enrolled as participants in HARMONY Outcomes U.S. sites. A U.S. site may participate in both the U.S. DataMart Strategy and/or the U.S. National Strategy.

\*\*\*Country selection considerations (dataset): 1) common person-level identifier, or equivalent data that can be used to link consented trial participants with national-level data 2) coverage of ~100% of defined population, and 3) availability of EHR events of interest

**Objective 1 – Qualitative Site Selection**

All HARMONY Outcomes sites (global) with an EHR will be invited to participate in the qualitative survey of Objective 1 of the ancillary study.

**Objectives 1 (Quantitative), 2, 3 – Technical Site Selection in the DataMart Strategy**

As part of the overall site selection process for the HARMONY Outcomes Trial, potential U.S. sites completed a feasibility survey to gauge their interest and suitability for participation in the technical components of the EHR Ancillary Study (ability to extract data from the EHR and transform to a common data format). The surveys included questions regarding experience with long-term outcome trials in general and specific features of the planned trial.

Key criteria used for selection of participating US sites for the technical components of Objectives 1 (Quantitative), 2, and 3 of the EHR-Ancillary Study include:

- Existence of an EHR
- Types of information currently contained in EHR;



- Current capability to extract EHR-type data from a data warehouse;
- Institutional processes and policies for using EHR-type data for clinical research;
- Institutional experience extracting, transforming, and loading warehouse data into a research DataMart that conforms with standardized specifications; and
- Access to an enterprise data warehouse or clinical data repository that stores structured data from the EHR and is updated at least weekly.
- Engagement of health system IT and analytical personnel

#### Objectives 2 and 3 – Technical National Partner Selection in the National Strategy

In select countries (Denmark, U.K. (England and Scotland), Sweden, Norway, and the United States), national partners will be asked to access existing national-level data sources to address Objectives 2 and 3. Key criteria used for the selection of participating countries include:

- Existence of an electronic health data source that covers either all of the national population or a defined population;
- Availability of a common person level identifier(s) or equivalent data that can be used to link consented trial participants with national-level data;
- Timely availability of information that can define the EHR events of interest (e.g. inpatient encounters and diagnoses, death or transfer out of population);
- An academic collaborator who has access and experience with the ethical, regulatory and technical requirements of using the data source

#### **11.7.3.4. Data Flows**

##### Qualitative Data Sources (Objective 1)

Objective 1 will survey study coordinators to obtain information on trial enrollment workflows, with a focus on how EHR systems are routinely used in the screening process, and what works best to facilitate this process. This objective will collect primary data through qualitative surveys and focus groups with study coordinators from participating sites to identify best practices and barriers to the use of EHR data for trial screening and enrolment.

First, a topic guide will be developed and tested with a small number of study coordinators to identify major survey themes. After revising and finalizing the guide, Webex focus groups will be conducted with coordinators to identify other relevant content. A report of findings will be generated based on a systematic analysis of the focus groups. A qualitative survey will then be developed based on topic guide testing, focus group report and feedback from survey experts and GSK team. The survey will be administered to study coordinators at participating sites. Survey data will then be analysed and a data report will be generated.

We will also conduct a qualitative assessment of enrollment “funnels” at the site level, where enrollment funnel is defined as the process by which the population of potentially eligible participants is narrowed to the final enrolled study population. This qualitative assessment will focus on reasons for non-enrollment among eligible patients at the site level. Each site will report the criteria used to generate the list of potentially eligible trial participants so that we can describe where the enrollment funnel begins and how it is narrowed down from potentially eligible subjects to those enrolled in the trial.

#### DataMart Strategy Data Flows (Objectives 1 [Quantitative], 2, and 3)

For the analyses based on technical components in Objectives 1, 2, and 3, select sites with technical capabilities participating in the EHR Ancillary Study will be required to convert relevant patient data from their EHR system into a Research DataMart, based on a common data model. A common data model standardizes the definition, content and format of data across sites to enable a single standardized view that can be used for querying. This is essential since EHR data are stored in different ways at different sites. The common data model for the ancillary study will be adapted from the PCORnet Common Data Model and may include the following data areas: demographics, encounters, diagnoses, procedures, and selected laboratory results. The study site’s EHR system will not be changed and will continue to operate as implemented. The Research DataMart includes Protected Health Information (PHI) and will remain behind institutional firewalls.

The methods for extracting useful information from the Research Datamart will require a partnership between study site teams (site principal investigator, site study coordinator, and site technical support), GSK, and the DCRI Data Management Team. The study will utilize secure mechanisms to distribute queries to participating sites and receive results. Many sites will use Aqueduct, a software application that enables the creation, operation, and governance of research networks. It allows partners to maintain physical and operational control over their data while allowing authorized users to send queries to the data.

The DCRI Data Management Team will distribute code that extracts and returns data for randomized participants from the Research DataMart. These data from randomized participants across all participating sites will make up a subset of the EHR Ancillary study dataset.

Required data elements of interest regarding baseline demographics and outcome events from the main HARMONY trial dataset will be transferred from GSK to DCRI after the completion of the study. DCRI will merge these data elements with the datamart EHR Ancillary study dataset.

#### National Strategy Data Flows (Objective 2 and 3)

Similarly, Objectives 2 and 3, as applied on the national level, will compare baseline characteristics and outcomes ascertained from the main HARMONY trial dataset with data from national electronic health data. However, the methods to access, extract and transfer data will be adapted to each participating country and will be guided by the expertise of the academic collaborator. Country specific methods will be used to 1)

access national-level electronic health data (for example, Medicare data in the U.S.), 2) use patient level identifier(s) to link HARMONY trial participants, and 3) transfer de-identified patient-level national electronic health data to DCRI to create the National Strategy EHR ancillary dataset and compare data elements of interest regarding baseline demographics and outcome events from the main HARMONY trial dataset. The final analysis dataset will be constructed after the end of the main HARMONY Outcomes trial and the data latency period, which is defined as the delay from the initial generation of EHR data or claims files to the availability of an analysis-ready dataset.

#### **11.7.4. DATA ANALYSIS**

##### **11.7.4.1. Sample Size Expectations**

The objectives of this ancillary study are exploratory (not confirmatory) in nature and not intended to be sufficiently powered to confirm a pre-determined level of sensitivity and specificity. The qualitative portion of Objective 1 will be open to participation from any interested Global site with an EHR. The technical components (datamarts) of Objectives 1, 2, and 3 of the ancillary study will target recruitment of ~7 U.S. sites, each recruiting 12-15 subjects, to support the study aims. The DataMart strategy will also utilize approximately 8 U.S. VA sites. The datasets generated using country-specific data for Objectives 2 and 3 are intended to include all randomized participants across HARMONY sites in each participating country.

##### **11.7.4.2. General Analytic Approach**

In Objective 1, the proportion of eligible patients identified by the computerized algorithm will be compared to the list of enrolled patients at participating sites. The goals of Objectives 2 and 3 involve evaluating the performance of algorithms that map EHR-based data into concepts present in the clinical trial dataset. Algorithms will be informed by general and therapeutic area-specific data standards, including the standards efforts of professional societies. Baseline characteristics and study endpoints in the ancillary study dataset will be defined using diagnosis codes and procedure codes. Published algorithms will be used whenever possible and these algorithms will be updated as necessary to account for coding changes since publication. The actual measures recorded in the clinical trial dataset will be considered the reference standard against which these measures based on technical components are compared.

For Objective 2, the performance of algorithms used to identify baseline characteristics will be evaluated. For Objective 3, the performance of algorithms used to identify trial events will be evaluated. Performance metrics will be calculated by site as well as across all sites. Within the national data used for Objectives 2 and 3, all performance metrics will be calculated by country as well as across all countries.

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## **11.8. Appendix 8: Country Specific Requirements**

## **11.9. Appendix 9: Protocol Amendment Changes**

### **11.9.1. Changes Resulting from Protocol Amendment 1**

This amendment is applicable to all participating countries.

#### **Summary of Changes**

1. Correction of typographical error in Exclusion criterion 7.
2. Clarification wording added to the description of when subjects should have telephone follow-up after discontinuing investigational product (IP). Subjects should have the telephone follow-up  $5 \pm 1$  weeks after their last dose of IP whether they had continued IP through to the Final study visit, or discontinued before the Final study visit.
3. Time and Event Table modified to add adverse event checking (SAE, AEs of special interest, AEs leading to IP discontinuation) to dose adjustment visits, and to correct footnote assignment/typographical errors.
4. Revision of terminology used to describe unstable angina events referred for CEC adjudication to correctly reflect review process to be adopted by CEC.
5. Addition of Country Specific Requirements appendix (Appendix 8).

#### **List of Specific Changes**

Section 4.2, Exclusion criteria; criterion 7, fourth sentence.

*Original text:*

Women who have developed spontaneous secondary amenorrhoea of 12 months or more where post-menopausal status is in doubt, a blood sample where FSH >40MU/ml and oestrodiol <40 pg/mL (<14 pmol/L) are simultaneously measured will be considered confirmatory.

*Amended text:*

Women who have developed spontaneous secondary amenorrhoea of 12 months or more where post-menopausal status is in doubt, a blood sample where FSH >40MU/ml and oestrodiol <40 pg/mL (<140 pmol/L) are simultaneously measured will be considered confirmatory.

Section 4.5 Procedures for Subject Follow-up*Original text:*

As described in Section 4.4, subjects who permanently discontinue investigational product will be asked to attend the clinic as soon as possible. They will continue in the study for follow-up. They will be asked to return to clinic according to the 8 monthly visit schedule and in addition be contacted by telephone at a time corresponding to the 4-monthly visit they would have otherwise made to replenish study medication supply. If instead of these interim telephone contacts the subject prefers to attend clinic every 4 months as originally scheduled that is an acceptable alternative.

*Amended text:*

As described in Section 4.4, subjects who permanently discontinue investigational product will be asked to attend the clinic as soon as possible. They will continue in the study for follow-up. ***Five weeks ( $\pm 1$  week) after discontinuation of investigational product, subjects will be contacted for a follow-up by telephone.*** They will be asked to return to clinic according to the 8 monthly visit schedule and in addition be contacted by telephone at a time corresponding to the 4-monthly visit they would have otherwise made to replenish study medication supply. If instead of these interim telephone contacts the subject prefers to attend clinic every 4 months as originally scheduled that is an acceptable alternative.

Table 1 Time and Events Table

*Original text:*

Procedures <sup>1,2</sup>	Screening <sup>2</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post and.)	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	Post-Study Follow up Phone Call 5 ± 1 weeks after last IP dose
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X		X	X	X

1. Subjects who discontinue investigational product should be handled as described in Section 4.4.

11. Study drug dispensing not performed at final visit, compliance check not performed at Screening.

*Amended text:*

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post <i>rand.</i> )	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	<del>Post-Study</del> Follow up Phone Call 5 ± 1 weeks after last IP dose
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X	X	X	X	X

1. Subjects who discontinue investigational product should be handled as described in Section 4.4 **and Section 4.5**.

11. Study drug dispensing not performed at final visit, compliance check not performed at **Randomisation**.



Section 6.2.1 Cardiovascular Events*Original text:*

The CEC will review and adjudicate the following clinical events:

Myocardial infarction

Stroke

Unstable angina requiring revascularization

Hospitalization for heart failure

Sudden cardiac death

TIA

In addition, all clinical events submitted for adjudication and all other SAEs with a fatal outcome will be reviewed and adjudicated to classify the cause of death as cardiovascular or non-cardiovascular.

*Amended text:*

The CEC will review and adjudicate the following clinical events:

Myocardial infarction

Stroke

***Unstable angina requiring hospitalization***

Hospitalization for heart failure

Sudden cardiac death

TIA

In addition, all clinical events submitted for adjudication and all other SAEs with a fatal outcome will be reviewed and adjudicated to classify the cause of death as cardiovascular or non-cardiovascular.

Appendix 8 – Country Specific Requirements

Appendix 8 added (not in original text). This is a blank page headed “11.8. Appendix 8: Country Specific Requirements” to serve as a placeholder to be replaced by each participating GSK Country Medical Department with the appropriate text upon receipt of the protocol and before they distribute it further within their country.

### 11.9.2. Changes Resulting from Protocol Amendment 2

This amendment is applicable to all participating countries (with the exception of item 8 below which is specific to Mexico).

#### Summary of Changes

1. Amendment to indicate that the study should be considered Phase III in countries where albiglutide has not been granted marketing authorisation and Phase IV in countries where it has been.
2. Update to list of protocol authors.
3. Update to Sponsor Medical Monitor Contact Information.
4. Correction of terminology in Treatment Assignment section.
5. Removal of discrepancy between inclusion criterion 4 which wrongly indicates a negative **serum** pregnancy test is required to exclude pregnancy and the Time & Event table (Section 6), Section 6.2.6 Clinical Laboratory Assessments, the model consent form and the Study Reference Manual (which all correctly indicate that the requirement is for a negative **urine** test).
6. Time and Event Table 1 re-formatted as some investigators had found it confusing.
7. Addition of a Time and Event table of assessments to be performed for patients permanently discontinuing IP (Table 2). The visits and telephone contact to be performed for patients discontinuing IP had been described in text previously but an additional tabular format was recommended to aid investigators.
8. Mexican Ministry of Health requirement to report events referred to CEC by Mexican investigators to also be reported to the Ministry as SAEs.
9. Addition of requirement to record lipid results if they are available from subjects' routine clinical care outside of the trial.
10. Clarify that TRIM-D should not be assessed at Baseline in subjects whose diabetes is treated by diet and exercise alone.
11. Corrections to Data Analysis and Statistical Considerations Section to make it more terminologically correct.
12. Simplification of description of information in Section 8.3.6.4 Other Safety Analyses to properly reflect the planned reports.
13. Correction of typographical error in spelling of spermicide.
14. Correction of recipient of faxed SAE reports if the electronic CRF is unavailable.

## List of Specific Changes

### Title Page

*Original text:*

Development Phase: IV

*Amended text:*

Development Phase: **III/IV**

*Original text:*

**Author (s):** The protocol was developed by the members of the Executive Committee in conjunction with Duke Clinical Research Institute and the Sponsor.

The following individuals provided substantial input during protocol development:

**Non-sponsor:** <sup>PPD</sup> [REDACTED] (Executive Committee Co-Chair);  
<sup>PPD</sup> [REDACTED] (Executive Committee Co-Chair); <sup>PPD</sup> [REDACTED]

**Sponsor:** <sup>PPD</sup> [REDACTED]

*Amended text:*

**Author (s):** The protocol was developed by the members of the Executive Committee in conjunction with Duke Clinical Research Institute and the Sponsor.

The following individuals provided substantial input during protocol development:

**Non-sponsor:** <sup>PPD</sup> [REDACTED] (Executive Committee Co-Chair); <sup>PPD</sup> [REDACTED]  
[REDACTED] (Executive Committee Co-Chair); <sup>PPD</sup> [REDACTED]

**Sponsor:** <sup>PPD</sup> [REDACTED]

### Sponsor Information Page, Sponsor Medical Monitor Contact Information

*Original text:*

#### **Sponsor Medical Monitor Contact Information:**

Dr <sup>PPD</sup> [REDACTED]  
2301 Renaissance Boulevard  
REN0410

King of Prussia, Pennsylvania 19406, USA

Email: PPD

Fax: PPD

Telephone number: Office: PPD

Cell: PPD

Out of hours: PPD

*Amended text:*

**Sponsor Medical Monitor Contact Information:**

Dr PPD

2301 Renaissance Boulevard

REN0410

King of Prussia, Pennsylvania 19406, USA

Email: PPD

Fax: PPD

Telephone number: Office: PPD

Cell: PPD

Out of hours: PPD

List of Abbreviations

*Original text:*

Did not include the abbreviations added in amendment.

*Amended text:*

HDLc	high density lipoprotein cholesterol
LDLc	low density lipoprotein cholesterol
Tg	triglycerides
TC	total cholesterol

Section 3.1 Overall Design, first paragraph

*Original text:*

This is a Phase IV, randomised, double blind, parallel-group, placebo-controlled, multicentre study.

*Amended text:*

This is a ~~Phase IV~~, randomised, double blind, parallel-group, placebo-controlled, multicentre study. ***In countries where marketing authorization has been granted to albiglutide for the treatment of type 2 diabetes it is classified as a Phase IV study, elsewhere it should be considered to be a Phase III study.***

Section 4.1 Inclusion Criteria; criterion 4, first sentence*Original text:*

Female: subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test for females of reproductive potential only), not breastfeeding, and at least one of the following conditions applies:

*Amended text:*

Female: subject is eligible to participate if she is not pregnant (as confirmed by a negative ~~serum~~ **urine** human chorionic gonadotrophin (hCG) test for females of reproductive potential only), not breastfeeding, and at least one of the following conditions applies:

Section 5.2 Treatment Assignment; final paragraph*Original text:*

Blinded study centre personnel will receive a randomisation notification indicating only the unique subject identifier and the date and time of randomisation. Each subject number will be a unique identifier. Once a subject number has been assigned, the number will not be reused even if the subject withdraws before receiving any investigational product. Details of the treatment assignment process are contained in the SRM.

*Amended text:*

Blinded study centre personnel will receive a randomisation notification indicating ~~only~~ the unique subject identifier (**randomisation number**) and the date and time of randomisation. Each **randomisation** subject number will be a unique identifier. Once a **randomisation** subject number has been assigned, the number will not be reused even if the subject withdraws before receiving any investigational product. Details of the treatment assignment process are contained in the SRM.

Table 1 Time and Events Table*Original text:*

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post rand.)	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	Follow up Phone Call 5 ± 1 weeks after last IP dose
Written informed consent	X							
Review of Inc/excl criteria	X	X						
Demography & directed medical history	X							
Assessment of MACE and micro-vascular events				X		X	X	
HbA1c	X <sup>5</sup>			X		X	X	
Serum creatinine (eGFR)	X <sup>5</sup>					X	X	
Liver Function Tests <sup>6</sup>		X				X	X	
Genetic sampling <sup>7</sup>		X						
Patient reported outcomes questionnaires <sup>8</sup>		X				X	X	
Key concomitant non-diabetes medication		X		X		X	X	X
Diabetes medication		X		X		X	X	X
Study drug reminder			X	X	X	X		
Physical examination <sup>9</sup>		X				X	X	
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X	X	X	X	X
Pregnancy test <sup>10</sup>	X	X						
Study drug dispense/compliance <sup>11</sup>		X		X	X	X	X	

- Subjects who discontinue investigational product should be handled as described in Section 4.4 and Section 4.5.
- Assessments per the Month 4 visit will alternate with those per the Month 8 visit throughout the study i.e., assessments at months 4, 12, 20 etc will be per Month 4; those at month 8, 16, 24 etc..will be per Month 8.
- Screening and Randomisation can occur at the same visit if all eligibility information is available. If Screening and Randomisation occur at the same visit assessments should not be duplicated.
- Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.
- HbA1c and creatinine assessed using local laboratories at Screening visit and measured no more than 6 months prior to randomisation. If HbA1c or creatinine have not been assessed in the previous 6 months assessments to be performed via a central laboratory and results available prior to randomization. The investigator has the discretion to repeat

- screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.
6. Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT. Blood samples for LFTs at randomization must be collected prior to the first dose of investigational product.
  7. Informed consent for genetic research must be obtained before collecting a sample. Genetics sample can be collected at any time after genetic consent has been obtained and the subject has been randomised.
  8. TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
  9. See Section 6.2.7.
  10. Only applies to women of child bearing potential. At screening perform urine pregnancy test. If positive, send serum sample to the central laboratory for confirmation. At Randomisation perform a urine pregnancy test. If result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised. If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. See Section 6.2.6.
  11. Study drug dispensing not performed at final visit, compliance check not performed at Randomisation

*Amended text:*

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post rand.)	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	Follow up Phone Call 5 ± 1 weeks after last IP dose
Written informed consent	X							
Review of Inc/excl criteria	X	X						
Demography & directed medical history	X							
Assessment of MACE and micro-vascular events				X		X	X	
HbA1c	X <sup>5</sup>			X		X	X	
Serum creatinine (eGFR)	X <sup>5</sup>			X (alternate visits) 2		X	X	
Liver Function Tests (LFTs) <sup>6</sup>		X		X (alternate visits) 2		X	X	
<b>Record available information on most recent lipid assessment<sup>7</sup></b>		X		X (annually)			X	
Genetic sampling <sup>7,8</sup>		X						
Patient reported outcomes questionnaires <sup>8,9</sup>		X <sup>10</sup>		X (alternate visits) 2		X	X	
Key concomitant non-diabetes medication		X		X		X	X	X

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post rand.)	Clinic Visit Month 4 ± 18 days then every 8 ± 4 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit* (or early withdrawal)	Follow up Phone Call 5 ± 1 weeks after last IP dose
Diabetes medication		X		X		X	X	X
Study drug reminder			X	X	X	X		
Physical examination <sup>9,11</sup>		X		X (alternate visits) 2		X	X	
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X	X	X	X	X
Pregnancy test <sup>10,12</sup>	X	X						
Study drug dispense/compliance <sup>11,13</sup>		X		X	X	X	X	

- Subjects who discontinue investigational product should be handled as described in Section 4.4 and Section 4.5 **and in Table 2.**
- ~~Assessments per the Month 4 visit will alternate with those per the Month 8 visit throughout the study i.e., assessments at months 4, 12, 20 etc will be per Month 4; those at month 8, 16, 24 etc. will be per Month 8.~~ **Assessments at month 8, 16, 24 etc. will include patient reported outcomes questionnaires, serum creatinine (eGFR), liver function tests and physical examination. Those at months 4, 12, 20 etc do not.**
- Screening and Randomisation can occur at the same visit if all eligibility information is available. If Screening and Randomisation occur at the same visit assessments should not be duplicated.
- Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.
- HbA1c and creatinine assessed using local laboratories at Screening visit and measured no more than 6 months prior to randomisation. If HbA1c or creatinine have not been assessed in the previous 6 months assessments to be performed via a central laboratory and results available prior to randomization. The investigator has the discretion to repeat screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.
- Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT. Blood samples for LFTs at randomization must be collected prior to the first dose of investigational product.
- Lipid values (TC, LDLc, HDLc, Tg) to be recorded as available from routine clinical care at baseline and annually thereafter. If results are unavailable, lipid tests are not to be performed for the study.**
- Informed consent for genetic research must be obtained before collecting a sample. ~~Genetics sample~~ **This** can be collected at any time after genetic consent has been obtained and ~~the subject has been randomised~~ **randomisation has occurred.**
- TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
- TRIM-D is not required for subjects whose diabetes is treated by diet and exercise alone at Baseline.
- See Section 6.2.7.
- Only applies to women of child bearing potential. At screening perform urine pregnancy test. If positive, send serum sample to the central laboratory for confirmation. At Randomisation perform a urine pregnancy test. If result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised. If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. See Section 6.2.6.
- Study drug dispensing not performed at final visit, compliance check not performed at Randomisation



Section 6 Study Assessments and Procedures; insertion of the following table after Table 1

**Table 2 Time and Events Table for Subjects Who Permanently Discontinue IP Prior to the End of the Study**

Procedures	Clinic visit as soon after permanent discontinuation of IP as possible	Phone Call 5 ± 1 week after last IP dose	Continue contact schedule established at randomisation 4 monthly ± 1 month. <i>Telephone</i> <sup>1,2</sup>	Continue contact schedule established at randomisation 4 monthly ± 1 month. <i>Clinic visit</i> <sup>1,3</sup>	Final study clinic visit <sup>4</sup>
Assessment of MACE and micro-vascular events	X		X	X	X
HbA1c	X			X	X
Serum creatinine (eGFR)	X			X	X
Liver Function Tests (LFTs) <sup>5</sup>	X			X	X
Record available information on most recent lipid assessment <sup>6</sup>	X		X (annually)	X (annually)	X
Patient reported outcomes questionnaire <sup>7</sup>	X				
Key concomitant non-diabetes medication	X	X	X	X	X
Diabetes medication	X	X	X	X	X
Physical examination <sup>8</sup>	X			X	X
AEs leading to IP discontinuation	X				
SAEs, AEs of special interest,	X	X	X	X	X
Study drug compliance	X				

1. After subjects permanently discontinue IP, follow-up should continue on the 4-monthly schedule established at randomisation.
2. Where a subject would have been scheduled to attend clinic at months 4, 12, 20, 28 etc after randomisation, a telephone contact will be performed instead (with assessments as shown above).
3. Where a subject would have been scheduled to attend clinic at months 8, 16, 24, 32 etc after randomisation, a clinic visit will be performed (with assessments as shown above). If a subject who has permanently discontinued IP is unable to attend clinic then they will be contacted by telephone instead and the telephone contact assessments will be performed.
4. Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.
5. Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT.
6. Lipid values (TC, LDLc, HDLc, Tg) to be recorded as available from routine clinical care annually. If results are unavailable, lipids tests are not to be performed for the study.
7. TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
8. See Section 6.2.7.

Section 6.2.1 Cardiovascular Events; footnote added to end of first sentence.*Original text:*

Events referred to the CEC by the investigator as potential endpoints or transient ischemic attacks (TIAs) will not be collected or reported as SAEs, regardless of the adjudication outcome (Section 6.2.2).

*Amended text:*

Events referred to the CEC by the investigator as potential endpoints or transient ischemic attacks (TIAs) will not be collected or reported as SAEs, regardless of the adjudication outcome (Section 6.2.2).<sup>1</sup>

## Footnote:

***<sup>1</sup> There is one exception to this statement. Per requirement of the Mexican Ministry of Health, all events referred to the CEC by Mexican investigators will also be submitted as SAEs to the Mexican Ministry of Health.***

Section 6.2.6 Clinical Laboratory Assessments; text to be inserted at end of sub-section***Lipids***

***Where serum lipid tests have been performed as part of the subject's routine clinical care (i.e. not as a study procedure) the most recent results should be recorded at baseline and annually thereafter. The lipid parameters to be recorded are total cholesterol (TC), low density lipoprotein cholesterol (LDLc), high density lipoprotein (HDLc) and triglycerides (Tg).***

***If any or all of these results are not already available from the subject's records then separate lipid tests should not be performed solely for the study.***

## Section 6.3.1.1. Treatment Related Impact Measure – Diabetes (TRIM-D)

*Original Text:*

In order to evaluate satisfaction with treatment and to compare satisfaction across treatment groups, the TRIM-D questionnaire will be self administered by all subjects at baseline and at each 8 month visit (and, to the extent possible, at the time of study completion or withdrawal from the study).

*Amended Text:*

In order to evaluate satisfaction with treatment and to compare satisfaction across treatment groups, the TRIM-D questionnaire will be self administered by all subjects at baseline (except for subjects whose diabetes is treated by diet and exercise alone) and all subjects at each 8 month visit (and, to the extent possible, at the time of study completion or withdrawal from the study).

Section 8.3.3.1 Primary Comparisons of Interest, second sentence*Original text:*

The primary endpoint will be the time to the first occurrence of MACE over the full duration of the study. A p-value for the primary endpoint will be calculated from a Cox regression model with treatment group as the only covariate for the hypotheses described in Section 8.1.

*Amended text:*

The primary endpoint will be the time to the first occurrence of MACE over the full duration of the study. A p-value for the primary endpoint will be calculated from a Cox **Proportional Hazards (PH)** regression model with treatment group as the only covariate for the hypotheses described in Section 8.1.

Section 8.3.3.2. Other Comparisons of Interest, insertion of two new sentences:*Original text:*

For other analyses incidence rates will be presented for binary data and summary statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous data. Furthermore, summary statistics of change from baseline for HbA1c will be presented along with percent of subjects within ranges of clinical interest (e.g., HbA1c < 7.0%).

*Amended text:*

For other analyses incidence rates will be presented for binary data and summary statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous data. **Time to event endpoints will be evaluated via the p-value from a Cox PH regression model with treatment as the only covariate.** Furthermore, summary statistics of change from baseline for HbA1c will be presented along with percent of subjects within ranges of clinical interest (e.g., HbA1c < 7.0%). **Available lipid data will be summarized for descriptive purposes.**

Section 8.3.6.2. Secondary Endpoint Analysis*Original text:*

Composite of the proportion of those achieving good control (HbA1c ≤ 7.0%) AND no severe hypoglycaemic incidents AND weight gain <5% at the end of the study would be evaluated utilize nonparametric, covariance-adjusted, extended Mantel-Haenszel tests. Additional analysis will be provided for scheduled visits. Nominal p-values and 95% CIs will be presented for these visits. Time to introduction of prandial insulin in those on basal insulin ± orals anti-hyperglycemic drugs at baseline will be analyzed using PH model / log-rank test and KM method similar to the primary endpoint.

Composite of microvascular events will be analyzed using a proportional Cox regression model / log-rank test and KM method similar to the primary endpoint.

*Amended text:*

Composite of the proportion of those achieving good control ( $HbA1c \leq 7.0\%$ ) AND no severe hypoglycaemic incidents AND weight gain  $<5\%$  at the end of the study would be evaluated utilize nonparametric, covariance-adjusted, extended Mantel-Haenszel tests. Additional analysis will be provided for scheduled visits. Nominal p-values and 95% CIs will be presented for these visits. Time to introduction of prandial insulin in those on basal insulin  $\pm$  orals anti-hyperglycemic drugs at baseline will be analyzed using **a Cox PH model** ~~/log-rank test~~ and KM method similar to the primary endpoint.

Composite of microvascular events will be analyzed using a proportional Cox regression model ~~/log-rank test~~ and KM method similar to the primary endpoint.

Section 8.3.6.4. Other Safety Analyses, paragraphs 3, 4 and 5.

*Original text:*

For SAEs, AEs leading to withdrawal and AEs of special interest occurring after discontinuation of investigational product, the number and percentage of subjects, total number of events, incidence density and event rate will be presented by treatment group and overall at the SOC, High Level Term and Preferred Term (PT) level. Relative Risk for each event and its 95% CI will also be presented. The time to first occurrence of the specific events and the time of the event with respect to the preceding dose of study medication will be summarized.

All cause mortality will be summarized by treatment group and analyzed using PH model similarly as the-primary endpoint.

All events sent to CEC (including TIAs) will be grouped by type based on the standard MedDRA queries that correspond to cardiovascular and cerebrovascular events. Adjudication results will be summarized by event type and treatment group. A by subject listing of these events will be generated. The listing will include seriousness, severity, whether event is a reason for early study drug discontinuation or study withdrawal, and adjudication results.

Pancreatitis events will be adjudicated by the independent Pancreatitis Adjudication Committee. The information for investigator reported pancreatitis events and its adjudication results will be provided.

*Amended text:*

For SAEs, AEs leading to **permanent IP** withdrawal and AEs of special interest ~~occurring after discontinuation of investigational product~~, the number and percentage of subjects, total number of events, **and** incidence density ~~and event rate~~ will be presented by treatment group and overall at the SOC, ~~High Level Term~~ and Preferred Term (PT) level. Relative Risk for each event and its 95% CI ~~will~~**may** also be presented **on a targeted basis**. The time to first occurrence of the specific events ~~and the time of the event with respect to the preceding dose of study medication~~ will be summarized.

All cause mortality will be summarized by treatment group and analyzed using *a Cox* PH model similarly as the primary endpoint.

All events sent to CEC (including TIAs) will be *summarized*. ~~grouped by type based on the standard MedDRA queries that correspond to cardiovascular and cerebrovascular events. Adjudication results will be summarized by event type and treatment group. A by subject listing of these events will be generated. The listing will include seriousness, severity, whether event is a reason for early study drug discontinuation or study withdrawal, and adjudication results.~~

Pancreatitis events will be adjudicated by the independent Pancreatitis Adjudication Committee. The information for investigator reported pancreatitis events and its adjudication results will be *summarized*~~provided~~.

#### Section 8.3.6.5 Value Evidence and Outcomes Analyses

##### Original Text:

TRIM-D total score and score for each domain will be summarized descriptively by treatment group and scheduled visit. Score changes from baseline will be compared between treatments for each visit by ANCOVA an model.

##### Amended Text:

TRIM-D total score and score for each domain will be summarized descriptively by treatment group and scheduled visit. Score changes from baseline will be compared between treatments for each visit by an ANCOVA ~~an~~ model.

#### Section 11.2 Appendix 2: GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP), final listed item

##### Original text:

8. Male condom **combined with a female** diaphragm, with or without a vaginal spermicide (foam, gel, film, cream, or suppository). In the UK it is a country-specific requirement of the regulatory authority (Medicines and Healthcare Products Regulatory Agency) that a vaginal spermicide be used.

##### Amended text:

8. Male condom **combined with a female** diaphragm, with or without a vaginal spermicide (foam, gel, film, cream, or suppository). In the UK it is a country-specific requirement of the regulatory authority (Medicines and Healthcare Products Regulatory Agency) that a vaginal ~~spermicide~~*spermicide* be used.

Section 11.5.5 Reporting of SAEs to GSK, edit to second bullet, insertion of new third bullet

*Original text:*

If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor or the SAE coordinator

*Amended text:*

If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the ~~Medical Monitor or the SAE coordinator~~**safety designee as detailed in the Study Reference Manual**

***The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.***

### **11.9.3. Changes Resulting from Protocol Amendment 3**

This amendment is applicable to all participating countries (with the exception of item 4 below which includes components specific to the countries listed).

#### **Summary of Changes**

1. Addition of requirement that the study achieve a median subject follow up of at least 1.5 years as well as the sample size derived number of primary endpoints.
2. Specifying that to meet the primary objective of assessing the effect of albiglutide with respect to MACE, the primary analysis will be non-inferiority. If the pre-specified non-inferiority criterion is met then superiority testing will be performed with a closed testing procedure. Previously, superiority testing of MACE was considered a secondary endpoint.
3. Removal of multiplicity testing strategy for selected secondary endpoints.
4. Revision of the data collection strategy for the exploratory electronic healthcare record ancillary study (Appendix 7) with improved clarity for the planned data flow and analytical approach. To be completed.

## List of Specific Changes

### Protocol Summary – Objectives/Endpoints

*Original text:*

Objectives	Endpoints
<b>Primary</b>	
To determine whether albiglutide is non-inferior with respect to MACE when added to glycaemic standard of care versus standard of care alone	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke) [Non-inferiority]</li> </ul>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li><b>Time to first occurrence of MACE [Superiority]</b><sup>(1 see footnote)</sup></li> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li><b>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start</b> <sup>(1 see footnote)</sup></li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li><b>The proportion of subjects achieving glycaemic control (HbA1c ≤ 7.0% at final assessment) with no severe hypoglycaemic incidents and weight gain &lt;5% of body weight</b> <sup>(1 see footnote)</sup></li> <li>The time to first occurrence of a clinically important microvascular event (see Section 6.2.4)</li> <li>Change in glycated haemoglobin (HbA1c)</li> <li>Change in body weight</li> <li>Patient reported outcomes from Treatment Related Impact Measures-D (TRIM-D)/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>All cause mortality</li> <li>Non-fatal serious adverse events (SAEs)</li> <li>Adverse events (AEs) leading to discontinuation of investigational product</li> <li>AE of special interest (see Section 6.2.3)</li> <li>Change in estimated glomerular filtration rate (eGFR) calculated using Modification of Diet in Renal Disease (MDRD) formula</li> <li>Change in blood pressure and heart rate</li> </ul>



1. If the primary endpoint meets the criteria for non-inferiority, a multiple comparisons adjustment strategy will be performed for these 3 secondary endpoints as specified in the Section 8.3.5.

*Amended text:*

Objectives	Endpoints
<b>Primary</b>	
<b>To assess the effect of albiglutide with respect to MACE when added to glycaemic standard of care versus standard of care alone</b>	<p><b>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke)</b></p> <p><b>The primary analysis will be non-inferiority. If the pre-specified non-inferiority criterion is met then superiority testing will be performed <sup>1</sup></b></p>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start</li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li>The proportion of subjects achieving glycaemic control (<math>HbA1c \leq 7.0\%</math> at final assessment) with no severe hypoglycaemic incidents and weight gain <math>&lt;5\%</math> of body weight</li> <li>The time to first occurrence of a clinically important microvascular event (see Section 6.2.4)</li> <li>Change in glycated haemoglobin (HbA1c)</li> <li>Change in body weight</li> <li>Patient reported outcomes from Treatment Related Impact Measures-D (TRIM-D)/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>All cause mortality</li> <li>Non-fatal serious adverse events (SAEs)</li> <li>Adverse events (AEs) leading to discontinuation of investigational product</li> <li>AE of special interest (see Section 6.2.3)</li> <li>Change in estimated glomerular filtration rate (eGFR) calculated using Modification of Diet in Renal Disease (MDRD) formula</li> <li>Change in blood pressure and heart rate</li> </ul>

1. As part of a closed testing procedure and therefore no adjustment will be made to the significance level (see Section 8.3.5)

Protocol Summary – Treatment Arms and Duration*Original text:*

The study will be event driven, i.e. follow up will continue until it is projected that approximately 611 adjudicated MACE events will have occurred. Consequently, the maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate, and is estimated to be between 3 and 5 years.

*Amended text:*

The study will continue until it is projected that at least 611 adjudicated MACE events will have occurred while requiring that the projected median duration of subject follow-up be at least 1.5 years. The maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate. If 611 events are reached before the estimated median duration of subject follow-up is projected to be at least 1.5 years, then the study will continue until it is predicted that the median subject follow-up time is at least 1.5 years. In that case more than 611 events would likely be observed.

Protocol Summary – Analysis*Original text:*

The study's primary question is whether albiglutide is non-inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. The primary analysis is an Intent-to-Treat (ITT) analysis of the time to the first occurrence of MACE using Cox's Proportional Hazard regression.

*Amended text:*

The study's primary question is whether albiglutide is non-inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. If non-inferiority is achieved, then superiority will be tested. The primary analysis is an Intent-to-Treat (ITT) analysis of the time to the first occurrence of MACE using Cox's Proportional Hazard regression.

## Section 2. Objectives and Endpoints

*Original text:*

Objectives	Endpoints
<b>Primary</b>	
To determine whether albiglutide is non-inferior with respect to MACE when added to glycaemic standard of care versus standard of care alone	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke) [Non-inferiority]</li> </ul>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li><b>Time to first occurrence of MACE [Superiority]</b><sup>(1 see footnote)</sup></li> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li><b>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start</b> <sup>(1 see footnote)</sup></li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li><b>The proportion of subjects achieving glycaemic control (HbA1c ≤ 7.0% at final assessment) with no severe hypoglycaemic incidents and weight gain &lt;5% of body weight</b> <sup>(1 see footnote)</sup></li> <li>The time to first occurrence of a clinically important microvascular event (see Section 6.2.4)</li> <li>Change in HbA1c</li> <li>Change in body weight</li> <li>Patient reported outcomes from TRIM-D/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>All cause mortality</li> <li>Non-fatal SAEs</li> <li>AEs leading to discontinuation of investigational product</li> <li>AE of special interest (see Section 6.2.3)</li> <li>Change in eGFR calculated using MDRD formula</li> <li>Change in blood pressure and heart rate</li> </ul>
<b>Exploratory</b>	
To evaluate patient reported experience of diabetes treatment	<ul style="list-style-type: none"> <li>Patient reported outcomes from study specific questionnaire</li> </ul>
To evaluate (at a subset of sites) barriers to using the	<ul style="list-style-type: none"> <li>Workflow impact of an EHR-generated list of subjects to</li> </ul>

Objectives	Endpoints
electronic health record (EHR) to facilitate trial enrolment and the quality of EHR data for use in populating baseline characteristics and identifying events of interest during trial follow-up. <sup>2</sup>	<p>facilitate trial enrolment.</p> <ul style="list-style-type: none"> <li>Concordance, sensitivity, specificity, and accuracy of baseline characteristics extracted from the EHR compared with those reported on the electronic case report form (eCRF)<sup>3</sup></li> <li>Concordance, sensitivity, specificity, and accuracy of EHR-identified events compared with study events<sup>3,4</sup></li> </ul>

1. If the primary endpoint meets the criteria for non-inferiority, a multiple comparisons adjustment strategy will be performed for these 3 secondary endpoints as specified in the Section 8.3.5.
2. Details are provided in a separate EHR ancillary study protocol (Appendix 7). Results from this exploratory investigation will be reported separately from the main clinical study report.
3. Comparison of EHR identified events with study events will be conducted in the same data subset.
4. Analyses to be undertaken after the main trial results are published.

*Amended text:*

Objectives	Endpoints
<b>Primary</b>	
<b>To assess the effect of albiglutide with respect to MACE when added to glycaemic standard of care versus standard of care alone</b>	<p><b>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke) [Non-inferiority]</b></p> <p><b>The primary analysis will be non-inferiority. If the pre-specified non-inferiority criterion is met then superiority testing will be performed<sup>1</sup></b></p>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start</li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li>The proportion of subjects achieving glycaemic control (HbA1c <math>\leq</math> 7.0% at final assessment) with no severe hypoglycaemic incidents and weight gain <math>&lt;</math>5% of body weight</li> <li>The time to first occurrence of a clinically important microvascular event (see Section 6.2.4)</li> <li>Change in HbA1c</li> <li>Change in body weight</li> <li>Patient reported outcomes from TRIM-D/EQ5D</li> </ul>

Objectives	Endpoints
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>• All cause mortality</li> <li>• Non-fatal SAEs</li> <li>• AEs leading to discontinuation of investigational product</li> <li>• AE of special interest (see Section 6.2.3)</li> <li>• Change in eGFR calculated using MDRD formula</li> <li>• Change in blood pressure and heart rate</li> </ul>
<b>Exploratory</b>	
To evaluate patient reported experience of diabetes treatment	<ul style="list-style-type: none"> <li>• Patient reported outcomes from study specific questionnaire</li> </ul>
To evaluate (at a subset of sites) barriers to using the electronic health record (EHR) to facilitate trial enrolment and the quality of EHR data for use in populating baseline characteristics and identifying events of interest during trial follow-up. <sup>2</sup>	<ul style="list-style-type: none"> <li>• Workflow impact of an EHR-generated list of subjects to facilitate trial enrolment.</li> <li>• Concordance, sensitivity, specificity, and accuracy of baseline characteristics extracted from the EHR compared with those reported on the electronic case report form (eCRF)<sup>3</sup></li> <li>• Concordance, sensitivity, specificity, and accuracy of EHR-identified events compared with study events <sup>3,4</sup></li> </ul>

1. As part of a closed testing procedure and therefore no adjustment will be made to the significance level (see Section 8.3.5)
2. Details are provided in a separate EHR ancillary study protocol (Appendix 7). Results from this exploratory investigation will be reported separately from the main clinical study report.
3. Comparison of EHR identified events with study events will be conducted in the same data subset.
4. Analyses to be undertaken after the main trial results are published.

### Section 3.1. Overall Design (5<sup>th</sup> paragraph)

#### *Original text:*

The study will be event driven, i.e., follow up will continue until it is projected that approximately 611 adjudicated MACE events will have occurred. Consequently, the maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate, and is estimated to be between 3 and 5 years. If the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years, respectively.

#### *Amended text:*

The study will continue until it is projected that at least 611 adjudicated MACE events will have occurred while requiring that the projected median duration of subject follow-up be at least 1.5 years. The maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate, and was originally estimated to be between 3 and 5 years. If the observed rate for MACE is 2.0%

or 3.0%, the mean follow-up will be 3.2 or 2.2 years, respectively. If the observed rate for MACE is sufficiently high such that the median subject follow-up would be less than 1.5 years then the study will continue until it is projected that the median follow-up is at least 1.5 years. In this scenario, the maximum duration of the study for an individual participant would be less than the 3 to 5 years originally estimated.

Section 3.3. Discussion of Design (3<sup>rd</sup> paragraph)

*Original text:*

The primary cardiovascular comparison will be to assess whether albiglutide is non-inferior to placebo with respect to time to first MACE.

*Amended text:*

The primary cardiovascular comparison will be to assess whether albiglutide is non-inferior to placebo with respect to time to first MACE. If non-inferiority is established, the time to first MACE for albiglutide compared to placebo will be tested for superiority.

Section 6, Table 1, footnote 4

*Original text:*

4. Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.

*Amended text:*

4. Once it is projected that the target number of MACE events will have been collected and that the estimated projected median duration of subject follow-up is at least 1.5 years, a 3 month window will be defined for conducting the final, face to face visit.

Section 6, Table 2, footnote 4

*Original text:*

4. Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.

*Amended text:*

4. Once it is projected that the target number of MACE events will have been collected and that the estimated projected median duration of subject follow-up is at least 1.5 years, a 3 month window will be defined for conducting the final, face to face visit.

## Section 8.1 Hypotheses

### *Original text:*

This trial will examine the following primary question:

- Whether albiglutide is non inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. Letting  $\lambda_1$  = hazard ratio for time to first MACE for albiglutide vs placebo, then:

Null hypothesis:  $\log \lambda_1 \geq \log(1.3)$

Alternative hypothesis:  $\log \lambda_1 < \log(1.3)$

### *Amended text:*

This trial will examine the following primary question:

- Whether albiglutide is non inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. Letting  $\lambda_1$  = hazard ratio for time to first MACE for albiglutide vs placebo, then:

Null hypothesis:  $\log \lambda_1 \geq \log(1.3)$

Alternative hypothesis:  $\log \lambda_1 < \log(1.3)$

- If non-inferiority is established, the effect on adjudicated MACE will be tested for superiority in a closed testing procedure. Letting  $\lambda_1$  = hazard ratio for time to first MACE for albiglutide vs placebo, then:

Null hypothesis:  $\log \lambda_1 \geq \log(1.0)$

Alternative hypothesis:  $\log \lambda_1 < \log(1.0)$

## Section 8.2.1 Sample Size Assumptions (2<sup>nd</sup> paragraph)

### *Original text:*

The power for MACE non-inferiority is calculated via the asymptotic variance and normality of the maximum likelihood estimator for the log-hazard ratio. Assuming a true hazard ratio of 1.0, 611 events will be needed to have 90% power to rule out non-inferiority margin of 1.3 for the hazard ratio with type I error of 0.05. The study duration will be event-driven. A total of 9400 subjects will be enrolled and followed until it is projected that approximately 611 adjudicated MACE events will have occurred. If the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years respectively, assuming that the number of subjects lost to follow-up accounts for 1% or less.

*Amended text:*

The power for MACE non-inferiority is calculated via the asymptotic variance and normality of the maximum likelihood estimator for the log-hazard ratio. Assuming a true hazard ratio of 1.0, 611 events will be needed to have 90% power to rule out non-inferiority margin of 1.3 for the hazard ratio with type I error of 0.05. A total of 9400 subjects will be enrolled and followed until it is projected that approximately 611 adjudicated MACE events will have occurred and the median duration of subject follow-up is estimated to be at least 1.5 years. If, for example, the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years respectively, assuming that the number of subjects lost to follow-up accounts for 1% or less.

Section 8.2.2 Sample Size Sensitivity for MACE non-inferiority*Original text:*

9400 subjects will be enrolled to cumulate the first MACE events experienced by 611 unique subjects. The study duration may vary depending on actual MACE event rate and duration of enrolment period.

**Table 3            Total Study Duration Sensitivity for Varying MACE Event Rate and Duration of Recruitment**

MACE rate (% pa)	Duration of recruitment			
	1.5 yrs	2.0 yrs	2.5 yrs	3.0 yrs
2.0	4.1yrs	4.4yrs	4.6yrs	4.9yrs
2.5	3.4 yrs	3.7yrs	3.9yrs	4.2yrs
3.0	3.0yrs	3.2yrs	3.5yrs	3.8yrs
3.5	2.7yrs	2.9yrs	3.2yrs	3.4yrs

*Amended text:*

9400 subjects will be enrolled to cumulate the first MACE events experienced by 611 unique subjects. The study duration may vary depending on actual MACE event rate and duration of enrolment period. If the estimated median duration of subject follow-up is less than 1.5 years at the time that 611 events have occurred then study will continue until it is estimated that the median duration of subject follow-up is at least 1.5 years.



**Table 3**      **Indicative\* Total Study Duration Sensitivity for Varying MACE Event Rate and Duration of Recruitment**

MACE rate (% pa)	Duration of recruitment			
	1.5 yrs	2.0 yrs	2.5 yrs	3.0 yrs
2.0	4.1yrs	4.4yrs	4.6yrs	4.9yrs
2.5	3.4 yrs	3.7yrs	3.9yrs	4.2yrs
3.0	3.0yrs	3.2yrs	3.5yrs	3.8yrs
3.5	2.7yrs	2.9yrs	3.2yrs	3.4yrs

\* Although indicative, other scenarios are possible

### Section 8.2.3 Sample Size Re-estimation

#### *Original text:*

The aggregate blinded event-rate data will be periodically reviewed by the Executive Committee and the sponsor. The study has an event-driven design. Should emerging data diverge significantly from protocol assumptions, the total sample size and/or follow up time may be adjusted, within the bounds of feasibility, to achieve the event target.

#### *Amended text:*

The aggregate blinded event-rate data will be periodically reviewed by the Executive Committee and the sponsor. The study has an event-driven design and also requires that the projected median duration of subject follow up be at least 1.5 years. Should emerging data diverge significantly from protocol assumptions, the total sample size and/or follow up time may be adjusted, within the bounds of feasibility, to achieve the event target.

### Section 8.3.3.1 Primary Comparisons of Interest

#### *Original text:*

The primary endpoint will be the time to the first occurrence of MACE over the full duration of the study. A p-value for the primary endpoint will be calculated from a Cox Proportional Hazards (PH) regression model with treatment group as the only covariate for the hypotheses described in Section 8.1.

The primary endpoint will be the time to the first occurrence of MACE over the full duration of the study. A p-value for non-inferiority of the primary endpoint will be calculated from a Cox Proportional Hazards (PH) regression model with treatment group

as the only covariate for the hypotheses described in Section 8.1. If non-inferiority is established, a p-value for superiority for the primary endpoint will be calculated from a Cox Proportional Hazards (PH) regression model with treatment group as the only covariate for the hypotheses described in Section 8.1.

#### Section 8.3.5 Multiplicity Controls

*Original text from start of 8.3.5 to before “Other Secondary Endpoints and Subgroup Analysis”, including diagram deleted and replaced with:*

*Amended text:*

If non-inferiority is established for the primary endpoint, the data will be used to test for evidence of superiority. This approach is a closed testing procedure, and therefore, no adjustment for multiplicity is required [Hung 2009].

#### Section 8.3.5 Multiplicity Controls (Other Secondary Endpoints and Subgroup Analysis)

*Original text:*

##### *Other Secondary Endpoints and Subgroup Analysis*

The following secondary endpoints will provide supportive evidence for cardiovascular safety and will not use any multiplicity adjustment procedure.

- Components of primary endpoint (MACE = cardiovascular death, MI, stroke)
- MACE + urgent revascularisation for unstable angina
- Cardiovascular death or hospitalisation for heart failure

Other secondary endpoints which do not qualify for formal statistical hypothesis testing will be analyzed and have results presented with confidence interval and nominal p-values:

- Mean HbA1c at scheduled visits and change from baseline
- Mean body weight at scheduled visits and change from baseline
- Mean eGFR at scheduled visits and change from baseline
- Time to initiation of prandial insulin
- Composite microvascular endpoint

To examine the degree of consistency of the overall treatment effect in terms of important prognostic factors, subgroup analyses of the primary outcomes will be performed based on subject demographics and baseline characteristics. These exploratory subgroup analyses will not be adjusted for multiple comparisons and will be interpreted descriptively.

*Amended text:*

*Other Secondary Endpoints and Subgroup Analysis*

The following secondary endpoints will provide supportive evidence for cardiovascular safety and metabolic efficacy and will not use any multiplicity adjustment procedure. Results will be presented with confidence interval and nominal p-values:

Components of primary endpoint (MACE = cardiovascular death, MI, stroke)

MACE + urgent revascularisation for unstable angina

Cardiovascular death or hospitalisation for heart failure

Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start

Time to initiation of prandial insulin in those subjects treated with basal insulin at study start.

The proportion of subjects achieving glycaemic control ( $\text{HbA1c} \leq 7.0\%$  at final assessment) with no severe hypoglycaemic incidents and weight gain  $<5\%$  of body weight

Mean HbA1c at scheduled visits and change from baseline

Mean body weight at scheduled visits and change from baseline

Mean eGFR at scheduled visits and change from baseline

Composite microvascular endpoint

To examine the degree of consistency of the overall treatment effect in terms of important prognostic factors, subgroup analyses of the primary outcomes will be performed based on subject demographics and baseline characteristics. These exploratory subgroup analyses will not be adjusted for multiple comparisons and will be interpreted descriptively.

Section 8.3.6.1 Primary Analysis (3<sup>rd</sup> and 4<sup>th</sup> paragraphs)

*Original text:*

The hypothesis of non-inferiority of albiglutide relative to placebo group with hazard ratio less than 1.3 with respect to cardiovascular risk will be tested at the end of the study when ~611 first MACE events are cumulated.

The strength of evidence for non-inferiority will be determined by testing the hypothesis that the observed hazard ratio is significantly different from the null margin of 1.3 (one-sided  $p < 0.025$  for such a test being equivalent to the upper 95% confidence limit after multiplicity adjustment for the hazard ratio being less than 1.3). The absolute risk difference per 100 PY and superiority p-value for albiglutide vs. placebo will also be presented.

*Amended text:*

The hypothesis of non-inferiority of albiglutide relative to placebo group with hazard ratio less than 1.3 with respect to cardiovascular risk will be tested at the end of the study. If non-inferiority is established, the hypothesis of superiority of albiglutide relative to placebo will be tested.

The absolute risk difference per 100 PY, with its associated 95% confidence interval, will also be presented.

Section 8.3.6.2 Secondary Endpoint Analysis*Deletion of 1<sup>st</sup> bullet which originally read:*

MACE superiority will be evaluated using the same Cox regression model as the primary analysis of MACE non-inferiority.

Section 10 References*Addition of following reference:*

Hung HMJ, Wang SJ. Some Controversial Multiple Testing Problems in Regulatory Applications, Journal of Biopharmaceutical Statistics 2009; 19:1, 1-11,

Appendix 7 Section 11.7.1.2 Literature Review*Original text:*

Electronic Health Records were primarily designed to document patient care and facilitate billing and reimbursement. The large amount of electronic data that are captured may also facilitate clinical research and public health surveillance.<sup>5</sup> Despite the complexity of EHR data, national networks have begun to use these data to improve public health and generate real-world evidence [Toh, 2012]. The Patient Centered Outcomes Research network (PCORnet) (pcornet.org) is a research network that is currently being designed to support observational comparative effectiveness research and clinical trials that are embedded in clinical care settings [Fleurence, 2014]. Similarly, the NIH Health Care Systems Research Collaboratory (nihcollaboratory.org) is creating infrastructure to improve the conduct of embedded clinical trials. One ongoing NIH Collaboratory trial is the Time to Reduce Mortality in End-Stage Renal Disease study (TiME) (clinicaltrials.gov identifier: NCT02019225). TiME is a large cluster-randomized, pragmatic trial that will evaluate the effects of systematic implementation of hemodialysis sessions of at least four hours versus usual hemodialysis care. The trial involves data acquisition from EHR systems through a partnership between academic investigators and two health care provider organizations with different electronic data systems. There are several other recent examples of clinical trials that were embedded in

health care delivery systems [Gulliford, 2014; van Staa, 2014]. For instance, one recent study evaluated the use of an electronic decision support tool to improve risk factor control (i.e., blood pressure and cholesterol) following a cerebrovascular event with outcome data collected from the EHR [Dregan, 2014]. While the specific intervention was not shown to be efficacious, data acquisition via EHR sources was robust and implemented at a low cost.

*Amended text:*

Electronic Health Records were primarily designed to document patient care and facilitate billing and reimbursement. The large amount of electronic data that are captured may also facilitate clinical research and public health surveillance. EHR data are inherently complex, originate from various settings (e.g., outpatient practices, hospitals, and laboratories) and may be inconsistently captured across systems. Despite the complexity of EHR data, national networks have begun to use these data to improve public health and generate real-world evidence [Toh, 2012]. The Patient Centered Outcomes Research network (PCORnet) (pcornet.org) is a research network that is currently being designed to support observational comparative effectiveness research and clinical trials that are embedded in clinical care settings [Fleurence, 2014]. Similarly, the NIH Health Care Systems Research Collaboratory (nihcollaboratory.org) is creating infrastructure to improve the conduct of embedded clinical trials. One ongoing NIH Collaboratory trial is the Time to Reduce Mortality in End-Stage Renal Disease study (TiME) (clinicaltrials.gov identifier: NCT02019225). TiME will examine optimal hemodialysis session length using data from EHR systems through a partnership between academic investigators and two health care provider organizations with different electronic data systems. There are several other recent examples of clinical trials that were embedded in health care delivery systems [Gulliford, 2014; van Staa, 2014]. For instance, one recent study evaluated the use of an electronic decision support tool to improve risk factor control (i.e., blood pressure and cholesterol) following a cerebrovascular event with outcome data collected from the EHR [Dregan, 2014]. While the specific intervention was not shown to be efficacious, data acquisition via EHR sources was robust and implemented at a low cost.

Appendix 7 Section 11.7.1.3 Ancillary Study Rationale

*Original text:*

Despite these earlier studies demonstrating the potential opportunities with EHR-based data acquisition, our understanding of how EHR-based platforms might increase the efficiency of data collection, outcome surveillance, and confirmation in an integrated manner is unknown. EHRs are inherently heterogeneous, with each implementation different from the next. The barriers to using EHR-generated lists of patients to facilitate trial enrolment, the fitness of EHR data for populating baseline characteristics in an electronic case report form (eCRF) and the use of EHR data to find events of interest during trial follow-up are not well characterized.

EHR systems contain a wealth of clinical data about patients who are connected to the health care delivery system and may be eligible for enrollment in a clinical trial. Anecdotal reports suggest that identification of potential patients using the EHR increases the number of patients to be screened but may not consistently translate to an increased number of patients enrolled. Causes are likely multi-factorial and may include the translatability of inclusion and exclusion criteria to structured clinical data, the algorithm used to identify potential patients, institutional restrictions regarding unsolicited patient contact, and others. There is a need to empirically assess the barriers to using an EHR-generated list of patients to facilitate trial enrollment.

Structured data captured in the EHR may be similar to data elements specified in baseline patient characteristics in the eCRF, yet EHR data are collected primarily to support clinical care and reimbursement needs. Their fitness for use as source data for selected data elements of the baseline patient characteristics in the eCRF has not been established.

During routine trial follow-up, study coordinators typically gather information from various sources including direct patient contact and medical records of the enrolling institution and outside facilities to document events for study participants. Evidence from the West of Scotland Coronary Prevention Study suggests that cardiovascular endpoints can be ascertained from routinely recorded EHR-type data, but classification was imperfect [Barry, 2013]. There is a need to specifically assess the utility of EHR data acquisition for follow-up events across multiple health systems.

In summary, the EHR is a rich source of clinical data, but is designed specifically to support clinical care delivery and reimbursement needs. The assumption that EHR data are fit for use in high-quality clinical research has not been rigorously evaluated. To provide evidence to address this knowledge gap, GlaxoSmithKline (GSK) and Duke Clinical Research Institute (DCRI) are committed to conducting an exploratory EHR Ancillary Study embedded within a large pragmatic clinical trial at selected study sites. The overarching goal is to further our understanding of how EHR data can be organized into a query-able format to facilitate a more efficient, reliable, and cost-effective research process. The proposed empirical work is exploratory in nature and both qualitative and quantitative.

*Amended text:*

Despite these earlier studies demonstrating the potential opportunities with EHR-based data acquisition, our understanding of how EHR-based platforms might increase the efficiency of data collection, outcome surveillance, and confirmation in an integrated manner is unknown. EHRs are inherently heterogeneous, with each implementation different from the next. The barriers to using EHR-generated lists of patients to facilitate trial enrolment, the fitness of EHR data for populating baseline characteristics in an electronic case report form (eCRF) and the use of EHR data to find events of interest during trial follow-up are not well characterized.

EHR systems contain a wealth of clinical data about patients who are connected to the health care delivery system and may be eligible for enrollment in a clinical trial. Anecdotal reports suggest that identification of potential patients using the EHR increases the number of patients to be screened but may not consistently translate to an increased

number of patients enrolled. Causes are likely multi-factorial and may include the translatability of inclusion and exclusion criteria to structured clinical data and the algorithm used to identify potential patients. There is a need to empirically assess the utility of using an EHR-generated list of patients to facilitate trial enrolment as well as understanding the barriers to use of an EHR system for enrolment.

Structured data captured in the EHR may be similar to data elements specified in baseline patient characteristics in the eCRF, yet EHR data are collected primarily to support clinical care and reimbursement needs. Their fitness for use as source data for selected data elements of the baseline patient characteristics in the eCRF has not been established.

During routine trial follow-up, study coordinators typically gather information from various sources including direct patient contact and medical records (some of which resides in electronic format, i.e., an EHR) of the enrolling institution and outside facilities to document events for study participants. There is a need to specifically assess the utility of EHR data acquisition for follow-up events across multiple health systems, and to address challenges to the future use of EHR as source data for global trials and observational studies.

In summary, the EHR is a rich source of clinical data that are increasingly used in pragmatic health research initiatives, but the assumption that EHR data are fit for use in high-quality clinical research has not been rigorously evaluated. To provide evidence to address this knowledge gap, GlaxoSmithKline (GSK) and Duke Clinical Research Institute (DCRI) are committed to conducting an exploratory EHR Ancillary Study alongside a large pragmatic clinical trial. The overarching goal is to further our understanding of how EHR data can be organized into a query-able format to facilitate a more efficient, reliable, and cost-effective research process. As a collaboration between an academic research institute and a pharmaceutical sponsor, this project provides a unique opportunity to compare electronic health record data with baseline characteristics and adjudicated events captured as part of a large, contemporary, outcomes-based trial.

#### Appendix 7 Section 11.7.2.1 Primary Objectives

*Original text:*

**Objective 1: Assess the barriers to using an EHR-generated list of patients to facilitate trial enrollment.**

Through site study coordinator surveys, workflow assessment, analysis of electronic screening logs, comparisons of enrolled patients with patients identified via algorithm, this retrospective objective will describe the screening “funnel” and identify factors responsible for narrowing the funnel from the pool of potentially eligible patients to those enrolled in the clinical trial. Barriers for using EHR systems for this purpose will be assessed at the site level and common cross-site themes will be identified.

**Objective 2: Evaluate the fitness of EHR data for use in populating the baseline characteristics in the eCRF**

After study completion and within selected data areas (e.g., demographics, medical history, concomitant medications), the level of agreement between data extracted from the EHR and data documented on the baseline eCRF (reference standard) will be evaluated. Additionally the performance of algorithms developed to identify comorbidities and other clinical concepts will be assessed at the site level and aggregated, where appropriate.

**Objective 3: Explore the use of EHR data to find events of interest during trial follow-up**

Case-finding algorithms will be developed for select specified endpoints (i.e., myocardial infarction, stroke, unstable angina, heart failure as outlined in the main study protocol), run during the conduct of the trial, and used to identify potential cases for follow-up by the study coordinator. The site study coordinator will record the dispensation of each potential case so that reconciliation can occur between eCRF documented events and EHR-generated potential events. Safety event reporting will proceed as outlined in the main study protocol (Main Protocol Section 6.2). At the conclusion of the study, the yield of case-finding algorithms will be evaluated along with the performance of EHR-based algorithms with eCRF-reported as well as adjudicated eCRF-reported events (reference standard).

*Amended text:*

**Objective 1: Understand how EHR data are used to facilitate trial recruitment and the barriers to that use..**

Using site study coordinator surveys, workflow assessment, qualitative analysis of a site-level enrollment measure, and quantitative comparisons of enrolled patients with potentially eligible patients, this objective will enhance understanding of how EHR data are used to facilitate clinical trial enrollment at global HARMONY sites with an EHR system and who express interest in participating. All global sites with an EHR will be invited to participate in the qualitative component – which will occur after main study enrollment is complete. For select sites in the United States, a quantitative analysis will be conducted comparing the proportion of eligible patients identified by a computerized algorithm to the site's list of enrolled patients. Algorithms will be developed based on structured data that represent trial inclusion criteria and submitted as a query to a subset of select sites with EHR systems that meet certain criteria and have technical capabilities.

**Objective 2: Evaluate the fitness of EHR data for use in populating the baseline characteristics in the eCRF**

For select sites, the level of agreement between data extracted from the EHR and data documented on the baseline eCRF (reference standard) will be evaluated and compared among consented participants. This will occur after study completion and within selected data areas (e.g., demographics, medical history, concomitant medications). Additionally



the performance of algorithms developed to identify comorbidities and other clinical concepts will be assessed at the site level and aggregated, where appropriate.

Other partnerships in select countries will support comparisons between data extracted from existing national-level electronic health data (or administrative claims data) and data documented on the baseline eCRF.

**Objective 3: Explore the use of EHR data to find events of interest during trial follow-up**

For select sites, case-finding algorithms will be developed for select specified endpoints (e.g., all-cause death, myocardial infarction, stroke, urgent revascularization for unstable angina, hospitalization for heart failure) and applied to EHR data. At the conclusion of the main HARMONY-Outcomes study, the performance of EHR algorithms will be compared with eCRF-reported and adjudicated eCRF-reported events (reference standard).

Other partnerships in select countries will support comparisons between data extracted from existing national-level electronic health data (or administrative claims data) and eCRF reported and adjudicated eCRF-reported events.

Appendix 7 Section 11.7.2.2 Secondary Objectives

*Has been deleted.*

Appendix 7 Section 11.7.3.1 Study Design

*Original text:*

The ancillary study will occur in the context of the HARMONY-Outcomes trial, a randomised, double blind, parallel-group, placebo-masked, controlled study to evaluate the effect of albiglutide on cardiovascular events in patients with Type 2 diabetes. Albiglutide will be administered subcutaneously once weekly in a population of patients with Type 2 diabetes and a previous history of cardiovascular disease and who do not have optimal glycaemic control). The duration of the ancillary study will mirror that of the HARMONY-Outcomes trial. The number of sites that will participate in the ancillary study depends upon the outcome of the site EHR capabilities assessment described in Section 11.7.3.2 (Site Selection) below. Five study sites recruiting 12-15 subjects each would enable a descriptive assessment of Objectives 1 and 2, whilst, if feasible, 500-1000 subjects at EHR-enabled sites would permit greater precision to be achieved in the assessment of Objective 3.

*Amended text:*

The ancillary study will be conducted in conjunction with the HARMONY-Outcomes trial, a randomised, double blind, parallel-group, placebo-masked, controlled study to evaluate the effect of albiglutide on cardiovascular events in patients with Type 2 diabetes. Albiglutide will be administered subcutaneously once weekly in a population of patients with Type 2 diabetes and a previous history of cardiovascular disease and who do not have optimal glycaemic control. The majority of research activities in the ancillary study will take place following the close of the HARMONY Outcomes Trial, with specified timelines laid out in objective-specific workplans. Data extracted from the EHR for the purpose of the ancillary study will cover the time period from randomization into the main HARMONY Outcomes Trial study through the end of that study. Objective 1 will include a qualitative survey for which all global sites with an EHR who express interest in participating will be invited to participate. In select sites, Objective 1 will also include the application of a screening algorithm to support the quantitative aspect of the analysis. For Objectives 2 and 3, select U.S. sites with specific technical capabilities will participate, as well as select countries where relevant national-level electronic health data are available and accessible.

#### 11.7.3.2. Data Flow Strategies – Introduction

The HARMONY EHR ancillary study will utilize two data flows, termed the DataMart and National strategies, to gather and analyze data. The DataMart strategy will support work done at select U.S. sites, in order to access electronic health record data from patients enrolled in the main HARMONY Outcomes trial at these sites. This strategy encompasses the quantitative section of Objective 1, as well as the entirety of Objectives 2 and 3. The National Strategy will support work done with global national partners, in order to access national electronic health data for patients enrolled in the main HARMONY Outcomes trial. This strategy will encompass only Objectives 2 and 3. More detailed information regarding these strategies can be found below in section 3.4.

#### Appendix 7 Section 11.7.3.2 Site Selection (amended to Section 11.7.3.3)

*Original text:*

Sites from the main trial will be selected to participate. As part of the overall site selection process for the main trial, potential sites complete a feasibility survey to gauge their suitability for participation in the HARMONY-Outcomes trial. In addition to questions regarding experience with long-term outcome trials in general and specific features of the planned trial, the feasibility survey includes questions about site readiness for an EHR-facilitated trial. Specific topics include:

- Existence of an EHR system;
- Current use of EHR to screen for potential study participants;

- Types of information currently contained in EHR (inpatient visits, outpatient visits, laboratory results, medications)
- Prior participation in a study that used EHR data for patient screening, follow-up, and/or data collection; and
- Local EHR support to assist with research studies.

Sites who meet minimum qualifications based on this survey (respond affirmatively regarding the existence of an EHR system and local EHR support to assist with research studies), and who have confirmed an interest in participating in the ancillary study will be approached for a more in-depth assessment of capabilities. Specific topics include:

- Current capability to extract EHR-type data from a data warehouse;
- Data domains currently included in the data warehouse (e.g., demographics, vital signs, diagnoses, procedures, medications prescribed, laboratory tests, and death);
- Coding terminologies used for each domain of data;
- Institutional processes and policies for using EHR-type data for clinical research;
- Institutional experience extracting, transforming, and loading warehouse data into a research DataMart that conforms with standardized specifications; and
- Familiarity with or participation in distributed research networks.

Subsequent structured discussions with individual sites may be necessary to explore capabilities and suitability for the ancillary study. For example, engagement of the health system's Information Technology (IT) personnel will be essential but is challenging to gauge in a written survey. Key site selection criteria include:

- Fully implemented EHR system
- Access to an enterprise data warehouse or clinical data repository that stores structured data from the EHR and is updated at least weekly.
- Availability of necessary data
- Engagement of health system IT and analytical personnel

The advantage of a multi-stage, rapid assessment of capabilities is that it allows for a relatively short feasibility survey that can be completed reliably by a study coordinator. Detailed technical questions are reserved for the individuals who provide EHR support for research studies.

*Amended text:*

**Table.4 HARMONY Outcomes Site and Country Participation by Ancillary Study Objective**

Objective	Sites			Select Countries
	Selected U.S. Sites with Technical Capabilities* (DataMart Strategy)	Global Sites with an Implemented EHR System	U.S. VA Sites	U.S.** and Global Partners*** (National Strategy)
1: Qualitative	X	X		
1: Quantitative	X		X	
2	X		X	X
3	X		X	X

\*Technical capabilities include ability to extract data from the EHR and transform to a common data format

\*\*The U.S. National Strategy will acquire Medicare Claims data for Medicare beneficiaries enrolled as participants in HARMONY Outcomes U.S. sites. A U.S. site may participate in both the U.S. DataMart Strategy and/or the U.S. National Strategy.

\*\*\*Country selection considerations (dataset): 1) common person-level identifier, or equivalent data that can be used to link consented trial participants with national-level data 2) coverage of ~100% of defined population, and 3) availability of EHR events of interest

#### Objective 1 – Qualitative Site Selection

All HARMONY Outcomes sites (global) with an EHR will be invited to participate in the qualitative survey of Objective 1 of the ancillary study.

#### Objectives 1 (Quantitative), 2, 3 – Technical Site Selection in the DataMart Strategy

As part of the overall site selection process for the HARMONY Outcomes Trial, potential U.S. sites completed a feasibility survey to gauge their interest and suitability for participation in the technical components of the EHR Ancillary Study (ability to extract data from the EHR and transform to a common data format). The surveys included questions regarding experience with long-term outcome trials in general and specific features of the planned trial.

Key criteria used for selection of participating US sites for the technical components of Objectives 1 (Quantitative), 2, and 3 of the EHR-Ancillary Study include:

- Existence of an EHR

- Types of information currently contained in EHR;
- Current capability to extract EHR-type data from a data warehouse;
- Institutional processes and policies for using EHR-type data for clinical research;
- Institutional experience extracting, transforming, and loading warehouse data into a research DataMart that conforms with standardized specifications; and
- Access to an enterprise data warehouse or clinical data repository that stores structured data from the EHR and is updated at least weekly.
- Engagement of health system IT and analytical personnel

#### Objectives 2 and 3 – Technical National Partner Selection in the National Strategy

In select countries (Denmark, U.K. (England and Scotland), Sweden, Norway, and the United States), national partners will be asked to access existing national-level data sources to address Objectives 2 and 3. Key criteria used for the selection of participating countries include:

- Existence of an electronic health data source that covers either all of the national population or a defined population;
- Availability of a common person level identifier(s) or equivalent data that can be used to link consented trial participants with national-level data;
- Timely availability of information that can define the EHR events of interest (e.g. inpatient encounters and diagnoses, death or transfer out of population);
- An academic collaborator who has access and experience with the ethical, regulatory and technical requirements of using the data source

#### Appendix 7 Section 11.7.3.3 Data Flows (amended to Section 11.7.3.4)

##### *Original text:*

The methods for data extraction and capture will require a partnership between study site teams (site principal investigator, site study coordinator, and site technical support), GSK, and the DCRI Data Management Team.

The study will utilize PopMedNet, a software application that enables the creation, operation, and governance of research networks. It allows partners to maintain physical and operational control over their data while allowing authorized users to send queries to the data. PopMedNet consists of two layers: a security layer where access controls and permissions are established and a layer of virtual pipes through which questions are sent from requestor to responder. The PopMedNet software consists of a web-based “network portal” and a DataMart Client application that is installed at each site. PopMedNet

employs a “publish-and-subscribe” architecture that does not require a hole through an institutional firewall, but rather allows institutions to pull a query behind the firewall for manual or automated execution.

In research networks with a common data model, PopMedNet is used to distribute executable code that institutions can choose to pull behind their firewall, run against the data in that appropriate format, and return results to the requestor. Security documentation will be provided to all participating sites.

The data flow for this ancillary study will be as follows:

- a) The study site’s EHR system will not be changed and will continue to operate as implemented. Data from the thousands of tables in the EHR will be integrated on a nightly basis into a data warehouse that supports research needs (the term EHR is used to mean the system that collects, displays, and stores transactional health care data).
- b) With guidance from the DCRI Data Management Team, the study site’s technical team will extract, transform, and load data from the enterprise data warehouse (or clinical data repository) to a Cohort DataMart according to the specifications of the common data model. A common data model standardizes the definition, content and format of data across sites to enable efficient, cross-site querying. The Cohort DataMart will be refreshed from the existing Data Warehouse on a biweekly basis. The Cohort DataMart includes Protected Health Information (PHI) for a broadly defined cohort of potential study participants and will remain behind institutional firewalls.
- c) Data from Pre-Screening logs completed as part of the main study will be captured in a database stored in the same area as the Cohort DataMart to facilitate characterization of the screening funnel. Data from the pre-screening log will enable comparisons of characteristics of potential participants identified via algorithm with patients screened and enrolled.
- d) When a participant is randomized into the study, the study coordinator will enter key subject identifiers (the main trial identifier (ID), Medical Record Number (MRN) equivalent, study randomization date) into the Key Identifier spread sheet.
- e) Via PopMedNet, the DCRI Data Management Team will distribute code that extracts data for randomized participants from the Cohort DataMart into the Study DataMart using the Key Identifier table. Trial ID and randomization date from the Key Identifier table will be included in the Study DataMart. Data for randomized patients at each site will be returned to the DCRI via the HARMONY-Outcomes trial EHR Ancillary Study Query Portal.
- f) Via PopMedNet, the DCRI will distribute executable code (e.g., SQL program) that will query the Study DataMart for potential study endpoints. [See Section a)b for case-finding algorithm].
- g) Potential cases (identified via case-finding algorithm) will be returned to the Study Coordinator who will record the dispensation of each potential case in the Case-finding Dispensation Log stored in the Study DataMart (i.e., recorded in the eCRF/not recorded in the eCRF and reasons).

- h) The Study DataMart containing randomized patient data will be transferred from each site to the DCRI on a regular basis (anticipated quarterly with specific frequency to be determined).

Required data elements from the main clinical trial dataset for EHR Ancillary Study sites will be transferred from GSK to the DCRI after the completion of the study. The DCRI will merge data elements from the main clinical trial dataset with Study DataMart data to create the EHR Ancillary Study Dataset.

*Amended text:*

#### Qualitative Data Sources (Objective 1)

Objective 1 will survey study coordinators to obtain information on trial enrollment workflows, with a focus on how EHR systems are routinely used in the screening process, and what works best to facilitate this process. This objective will collect primary data through qualitative surveys and focus groups with study coordinators from participating sites to identify best practices and barriers to the use of EHR data for trial screening and enrolment.

First, a topic guide will be developed and tested with a small number of study coordinators to identify major survey themes. After revising and finalizing the guide, Webex focus groups will be conducted with coordinators to identify other relevant content. A report of findings will be generated based on a systematic analysis of the focus groups. A qualitative survey will then be developed based on topic guide testing, focus group report and feedback from survey experts and GSK team. The survey will be administered to study coordinators at participating sites. Survey data will then be analysed and a data report will be generated.

We will also conduct a qualitative assessment of enrollment “funnels” at the site level, where enrollment funnel is defined as the process by which the population of potentially eligible participants is narrowed to the final enrolled study population. This qualitative assessment will focus on reasons for non-enrollment among eligible patients at the site level. Each site will report the criteria used to generate the list of potentially eligible trial participants so that we can describe where the enrollment funnel begins and how it is narrowed down from potentially eligible subjects to those enrolled in the trial.

#### DataMart Strategy Data Flows (Objectives 1 [Quantitative], 2, and 3)

For the analyses based on technical components in Objectives 1, 2, and 3, select sites with technical capabilities participating in the EHR Ancillary Study will be required to convert relevant patient data from their EHR system into a Research DataMart, based on a common data model. A common data model standardizes the definition, content and format of data across sites to enable a single standardized view that can be used for querying. This is essential since EHR data are stored in different ways at different sites. The common data model for the ancillary study will be adapted from the PCORnet Common Data Model and may include the following data areas: demographics, encounters, diagnoses, procedures, and selected laboratory results. The study site’s EHR system will not be changed and will continue to operate as implemented. The Research

DataMart includes Protected Health Information (PHI) and will remain behind institutional firewalls.

The methods for extracting useful information from the Research Datamart will require a partnership between study site teams (site principal investigator, site study coordinator, and site technical support), GSK, and the DCRI Data Management Team. The study will utilize secure mechanisms to distribute queries to participating sites and receive results. Many sites will use Aqueduct, a software application that enables the creation, operation, and governance of research networks. It allows partners to maintain physical and operational control over their data while allowing authorized users to send queries to the data.

The DCRI Data Management Team will distribute code that extracts and returns data for randomized participants from the Research DataMart. These data from randomized participants across all participating sites will make up a subset of the EHR Ancillary study dataset.

Required data elements of interest regarding baseline demographics and outcome events from the main HARMONY trial dataset will be transferred from GSK to DCRI after the completion of the study. DCRI will merge these data elements with the datamart EHR Ancillary study dataset.

#### National Strategy Data Flows (Objective 2 and 3)

Similarly, Objectives 2 and 3, as applied on the national level, will compare baseline characteristics and outcomes ascertained from the main HARMONY trial dataset with data from national electronic health data. However, the methods to access, extract and transfer data will be adapted to each participating country and will be guided by the expertise of the academic collaborator. Country specific methods will be used to 1) access national-level electronic health data (for example, Medicare data in the U.S.), 2) use patient level identifier(s) to link HARMONY trial participants, and 3) transfer de-identified patient-level national electronic health data to DCRI to create the National Strategy EHR ancillary dataset and compare data elements of interest regarding baseline demographics and outcome events from the main HARMONY trial dataset. The final analysis dataset will be constructed after the end of the main HARMONY Outcomes trial and the data latency period, which is defined as the delay from the initial generation of EHR data or claims files to the availability of an analysis-ready dataset.

#### Appendix 7 Section 11.7.4.1 Sample Size Expectations

##### *Original text:*

The objectives of this ancillary study are exploratory (not confirmatory) in nature and not intended to be sufficiently powered to confirm a pre-determined level of sensitivity and specificity. The number of sites and subjects that will participate in the ancillary study depends upon the outcome of the site EHR capabilities assessment described in Section 11.7.3.2 (Site Selection). Five study sites recruiting 12-15 subjects each would enable a



descriptive assessment of Objectives 1 and 2, whilst, if feasible, 500-1000 subjects at EHR-enabled sites would permit greater precision to be achieved in the assessment of Objective 3.

*Amended text:*

The objectives of this ancillary study are exploratory (not confirmatory) in nature and not intended to be sufficiently powered to confirm a pre-determined level of sensitivity and specificity. The qualitative portion of Objective 1 will be open to participation from any interested Global site with an EHR. The technical components (datamarts) of Objectives 1, 2, and 3 of the ancillary study will target recruitment of ~7 U.S. sites, each recruiting 12-15 subjects, to support the study aims. The DataMart strategy will also utilize approximately 8 U.S. VA sites. The datasets generated using country-specific data for Objectives 2 and 3 are intended to include all randomized participants across HARMONY sites in each participating country.

Appendix 7 Section 11.7.4.2 deleted.

*Original text:*

Because any survey administered for this objective will be a site-level survey, analysis of the survey data will be performed across all sites. For quantities of interest, frequencies with percentages for categorical measures and means with standard deviations for continuous measures will be presented.

Appendix 7 Section 11.7.4.3 (now 11.7.4.2) renamed General Analytical Approach (was General Analytic Approach for Objective 1 and Objective 2)

*Original text:*

The goals of both Objective 2 and Objective 3 involve evaluating the performance of algorithms that map EHR-based data into concepts present in the clinical trial dataset. The actual measures recorded in the clinical trial dataset will be considered the reference standard against which these algorithm-based measures are compared.

**Table 4 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Categorical variables**

New measure (EHR Ancillary Study data)	Reference standard (Clinical trial data)	
	Condition present	Condition absent
Condition present	True positive (TP)	False positive (FP)
Condition absent	False negative (FN)	True negative (TN)

For categorical variables, estimated performance metrics will be based on the 2x2 cross-tabulation of values in the EHR Ancillary Study dataset with values in the clinical trial dataset (Table 4) and include:

- Overall agreement =  $(TP + TN) / (TP + FP + FN + TN)$
- Sensitivity =  $TP / (TP + FN)$
- Specificity =  $TN / (FP + TN)$
- Positive predictive value =  $TP / (TP + FP)$
- Negative predictive value =  $TN / (FN + TN)$
- Accuracy or efficiency =  $(TP + TN) / (TP + TN + FP + FN)$

For dichotomous measures, each of these proportions is immediately calculable. For measures having more than two levels, multiple dichotomous measures will be created in order to calculate these proportions. Confidence intervals (95%) will be reported around these quantities. (See Table 5 as an example).

**Table 5 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Categorical variables**

Measure	Overall agreement (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Measure 1	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
Measure 2	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
.....	.....	.....	.....	.....	.....

Reported on 0–100 scale

For continuous measures, bias will be calculated as the difference between values in the EHR Ancillary Study dataset and values in the clinical trial dataset. The mean and

standard deviation of the bias along with a 95% confidence interval will be reported. In Bland-Altman analyses of agreement between continuous measures, the standard deviation of the bias is referred to as the precision, while the 95% confidence interval is referred to as the limit of agreement. (See Table 6 as an example).

**Table 6 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Continuous variables**

Measure	Bias	
	Mean (SD)	95% (CI)
Measure 1	XX.X	XX.X
Measure 2	XX.X	XX.X
.....	.....	.....

Due to the nature of EHR data, it is expected that there will be systematic differences between sites with respect to coding of clinical concepts. All performance metrics will therefore initially be calculated by site. These site-specific results may be best reported graphically.

There is also interest in an assessment of algorithm performance across all sites. Hierarchical models will be used to combine data from all sites and estimate performance at the “average” site. To estimate proportions (e.g. for overall agreement, sensitivity, specificity, etc. associated with categorical measures), models will be specified as:

$$\text{logit}(E(y)) = \beta_0 + \gamma_{0,j}$$

$$\gamma_{0,j} \sim N(0, s^2)$$

where sites are indexed by  $j$ . The value of the proportion at the average site—when  $\gamma_0=0$ —is  $[1 + \exp(-\beta_0)]^{-1}$ . Patients included in the estimation of each model vary by performance metric and reflect the definitions above. As an example, consider positive predictive value. To estimate the positive predictive value of an algorithm, only subjects with true positive value and false positive values will be included. True positives will be assigned  $Y=1$  and false positive will be assigned  $Y=0$ .

To estimate means (e.g. for bias associated with continuous variables), the model will be specified as:

$$E(y) = \beta_0 + \gamma_{0,j}$$

$$\gamma_{0,j} \sim N(0, s^2)$$

The value of the mean at the average site is  $\beta_0$ .

For all models, we will assess site heterogeneity by testing if  $s^2=0$ .

*Amended text:*

In Objective 1, the proportion of eligible patients identified by the computerized algorithm will be compared to the list of enrolled patients at participating sites. The goals of Objectives 2 and 3 involve evaluating the performance of algorithms that map EHR-based data into concepts present in the clinical trial dataset. Algorithms will be informed by general and therapeutic area-specific data standards, including the standards efforts of professional societies. Baseline characteristics and study endpoints in the ancillary study dataset will be defined using diagnosis codes and procedure codes. Published algorithms will be used whenever possible and these algorithms will be updated as necessary to account for coding changes since publication. The actual measures recorded in the clinical trial dataset will be considered the reference standard against which these measures based on technical components are compared.

For Objective 2, the performance of algorithms used to identify baseline characteristics will be evaluated. For Objective 3, the performance of algorithms used to identify trial events will be evaluated. Performance metrics will be calculated by site as well as across all sites. Within the national data used for Objectives 2 and 3, all performance metrics will be calculated by country as well as across all countries.

Appendix 7 Section 11.7.4.4 & Section 11.7.4.5 deleted*Original text:***11.7.4.4. Objective 2: Evaluate the Fitness of EHR Data for Use in Populating the Baseline Characteristics in the eCRF**

Algorithms will be defined to map EHR-based data in the Study Data Mart to specific concepts in the EHR Ancillary Study dataset that parallel concepts in the clinical trial dataset. For Objective 2, the performance of algorithms used to identify baseline characteristics will be evaluated. The baseline characteristic measures recorded in the clinical trial dataset will be considered the reference standard against which these algorithm-based measures are compared.

**11.7.4.5. Objective 3: Explore the Use of EHR Data to Find Events of Interest During Trial Follow-up**

Algorithms will be defined to map EHR-based data in the Study Data Mart to specific concepts in the EHR Ancillary Study dataset that parallel concepts in the clinical trial dataset. For Objective 3, the performance of algorithms used to identify trial events will be evaluated. These algorithms will be evaluated against both the adjudicated events recorded in the clinical trial dataset and the identified potential events in the eCRF. For each event, estimates of sensitivity and positive predictive value (described in Section 11.7.4.3) will be calculated and presented with 95% confidence intervals.

## TITLE PAGE

**Division:** Worldwide Development

**Information Type:** Protocol Amendment

<b>Title:</b>	A long term, randomised, double-blind, placebo-controlled study to determine the effect of albiglutide, when added to standard blood glucose lowering therapies, on major cardiovascular events in patients with Type 2 diabetes mellitus. Harmony Outcomes Trial.
---------------	--

**Compound Number:** GSK716155

**Development Phase:** III/IV

**Effective Date:** 22-JUL-2015

**Protocol Amendment Number:** 02

**Author (s):** The protocol was developed by the members of the Executive Committee in conjunction with Duke Clinical Research Institute and the Sponsor.

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**Revision Chronology**

<b>GlaxoSmithKline Document Number</b>	<b>Date</b>	<b>Version</b>
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<p>Clarification added regarding follow-up after discontinuation of investigational product.</p> <p>Addition of safety assessment to dose adjustment visits.</p> <p>Addition of Country Specific Requirements appendix.</p> <p>Correction of typographical errors and inconsistent terminology.</p>		
2014N193553_02	2015-JUL-22	Amendment No. 2
<p>Amendment to study phase for participating countries where albiglutide is not licensed.</p> <p>Update list of Authors.</p> <p>Update to Sponsor Information</p> <p>Removal of discrepancy in level of pregnancy testing required for inclusion.</p> <p>Reformatting of Time and Event table to improve clarity.</p> <p>Addition of table of visits for subjects discontinuing investigational product (previously included in text) as an aid to investigators.</p> <p>Addition of requirement of Mexican Ministry of Health to report events referred to Clinical Endpoint Committee from Mexican investigators as Serious Adverse Events.</p> <p>Addition of requirement to record lipid results if they are available from subjects' routine clinical care outside of the trial.</p> <p>Clarify that TRIM-D should not be assessed at Baseline in subjects whose diabetes is treated by diet and exercise alone.</p> <p>Simplification of description of safety analyses to properly reflect the planned reports.</p> <p>Correction of typographical and process errors.</p>		

**SPONSOR SIGNATORY**

PPD



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22 July 2015

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Date

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**Regulatory Agency Identifying Number(s):**

Investigational New Drug (IND) Number: IND65177  
European Drug Regulatory Authorities Clinical Trials (EudraCT) No. 2014-001824-32.



**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

For protocol number GLP116174

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature	Date	

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## LIST OF ABBREVIATIONS

ACCF	American College of Cardiology Foundation
ADA	American Diabetes Association
AE	adverse event
AHA	American Heart Association
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANCOVA	analysis of covariance
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BI	baseline basal insulin population
BMI	body mass index
bpm	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEC	Cardiovascular Endpoint Committee
CI	confidence interval
CPK	creatine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
DCRI	Duke Clinical Research Institute
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EHR	electronic health record
ESC	European Society of Cardiology
FDA	US Food and Drug Administration
FRP	females of reproductive potential
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GSK	GlaxoSmithKline
HbA1c	glycated haemoglobin
hCG	human chorionic gonadotrophin
HDLc	high density lipoprotein cholesterol
HLA	human leukocyte antigen
HRT	hormone replacement therapy
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normal range
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	Interactive Voice Response System

KM	Kaplan-Meier
LDH	lactate dehydrogenase
LFT	liver function test
LDLc	low density lipoprotein cholesterol
MACE	major adverse cardiovascular event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MSDS	Material Safety Data Sheet
MTC	medullary thyroid cancer
NHLBI	National Heart, Lung and Blood Institute
NI	non-insulin population
PAD	peripheral arterial disease
PD	pharmacodynamics
PHI	Protected Health Information
PK	pharmacokinetics
PP	per protocol
RAP	Reporting Analysis Plan
RR	relative risk
s.c.	subcutaneous
SAE	serious adverse event
SRM	Study Reference Manual
SU	sulfonylureas
TC	total cholesterol
Tg	triglycerides
TIA	transient ischemic attack
TRIM-D	Treatment Related Impact Measures-D
ULN	upper limit of normal range
WHF	World Heart Federation
WHO	World Health Organization

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## PROTOCOL SUMMARY

### Rationale

Albiglutide is a novel analogue of glucagon-like peptide-1 (GLP-1) with a sufficiently long half-life to permit once a week injection. Albiglutide is licensed for the treatment of type 2 diabetes as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies, including basal insulin. The Food and Drug Administration (FDA) has issued guidance on evaluating cardiovascular risk in new anti-diabetic therapies to treat type 2 diabetes [FDA [Guidance for Industry](#), 2008]. For a premarketing application that contains a meta-analysis of major adverse cardiovascular events (MACE) for which the upper bound of the 95 percent confidence interval for the relative risk is between 1.3 and 1.8, a post-marketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. The MACE meta-analysis of the albiglutide Phase III program (primary endpoint cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina), whilst ruling out an upper bound of the confidence interval for cardiovascular events of 1.8, was not able to rule out (due to a relatively small number of events) a relative risk (RR) upper bound of 1.3. For this reason GlaxoSmithKline (GSK) will conduct this cardiovascular outcome study as a US post-marketing requirement, to evaluate the effect of albiglutide on cardiovascular events in subjects with type 2 diabetes.

### Objectives/Endpoints

Objectives	Endpoints
<b>Primary</b>	
To determine whether albiglutide is non-inferior with respect to MACE when added to glycaemic standard of care versus standard of care alone	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke) [Non-inferiority]</li> </ul>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE [Superiority]<sup>(1 see footnote)</sup></li> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start <sup>(1 see footnote)</sup></li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li>The proportion of subjects achieving glycaemic control (HbA1c ≤ 7.0% at final assessment) with no severe hypoglycaemic incidents and weight gain &lt;5% of body weight <sup>(1 see footnote)</sup></li> <li>The time to first occurrence of a clinically important microvascular event (see Section 6.2.4)</li> <li>Change in glycated haemoglobin (HbA1c)</li> <li>Change in body weight</li> </ul>



Objectives	Endpoints
	<ul style="list-style-type: none"> <li>• Patient reported outcomes from Treatment Related Impact Measures-D (TRIM-D)/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>• All cause mortality</li> <li>• Non-fatal serious adverse events (SAEs)</li> <li>• Adverse events (AEs) leading to discontinuation of investigational product</li> <li>• AE of special interest (see Section 6.2.3)</li> <li>• Change in estimated glomerular filtration rate (eGFR) calculated using Modification of Diet in Renal Disease (MDRD) formula</li> <li>• Change in blood pressure and heart rate</li> </ul>

1. If the primary endpoint meets the criteria for non-inferiority, a multiple comparisons adjustment strategy will be performed for these 3 secondary endpoints as specified in the Section 8.3.5.

## Overall Design

This is a randomised, double blind, parallel group, placebo-controlled study.

## Treatment Arms and Duration

All subjects will receive standard of care for their diabetes and cardiovascular health which can be adjusted by the healthcare professional responsible for the subject during the study according to clinical need and with close adherence to professional society treatment guidelines. The study comparison is thus between albiglutide added to standard of care and standard of care alone. Placebo injections will be used to ensure study assessments are performed without knowledge of treatment assignment. Treatment with albiglutide or placebo will be randomly allocated in a 1:1 ratio. The starting dose of albiglutide is 30 mg weekly which may be up-titrated to 50mg weekly if further improvement of glycaemic control is required.

The study will be event driven, i.e. follow up will continue until it is projected that approximately 611 adjudicated MACE events will have occurred. Consequently, the maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate, and is estimated to be between 3 and 5 years.

An Independent Data Monitoring Committee (IDMC) will have study oversight to ensure participant safety and scientific integrity of the data.

## Type and Number of Subjects

A total of 9400 subjects with type 2 diabetes and a previous history of cardiovascular disease and who do not have optimal glycaemic control will be studied.

## Analysis

The study's primary question is whether albiglutide is non-inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. The primary analysis is an Intent-to-Treat (ITT)

analysis of the time to the first occurrence of MACE using Cox's Proportional Hazard regression.

## 1. INTRODUCTION

### 1.1. Background

Diabetes affects an estimated 347 million people worldwide, with type 2 diabetes accounting for more than 90% of cases [[WHO](#), 2013]. The primary manifestation of this disease is chronic hyperglycaemia, resulting from resistance to insulin action at a cellular and molecular level and a relative inadequacy in the secretion of endogenous insulin [[American Diabetes Association](#), 2014]. Chronic hyperglycaemia has been firmly established as a key factor in the development of microvascular complications (retinopathy, nephropathy, and neuropathy). Individuals with type 2 diabetes are also at greatly elevated risk of cardiovascular disease.

The management of glycaemia in individuals with type 2 diabetes consists of diet, exercise, and weight reduction together with oral anti-diabetic drug, injectable agents such as GLP-1 receptor agonists or insulin therapy, to achieve near normoglycaemia as reflected by a target HbA1c level of  $\leq 7\%$ , where possible, without significant hypoglycaemia or other adverse effects of treatment. Despite the large number of available therapeutic agents, a high proportion of subjects fail to achieve or maintain target HbA1c levels [[Khunti](#), 2013] owing to the inexorable decline in endogenous insulin production characteristic of the disease, and limitations in existing treatments. New agents with complementary mechanisms (permitting combination use) or more favourable safety profiles are needed to help more subjects achieve glycaemic targets.

GLP-1 is secreted by intestinal L-cells in response to ingestion of food. In a healthy individual, it plays an important role regulating postprandial blood glucose by stimulating glucose-dependent insulin secretion by the pancreas. GLP-1 suppresses glucagon secretion, leading to reduced hepatic glucose output. It also delays gastric emptying time and slows small bowel motility, delaying food absorption and slowing the rate of glucose appearance in the blood. In patients with type 2 diabetes the postprandial rise in endogenous GLP-1 is absent or reduced [[Vilsbøll](#), 2001].

GLP-1 receptor agonists have been developed as anti-hyperglycemic therapy for type 2 diabetes to replace or supplement endogenous GLP-1 in order to increase meal-related insulin secretion, reduce inappropriate glucagon secretion, and slow GI motility. They have demonstrated substantial effectiveness in improving glycaemic control while mitigating the risk of hypoglycaemia and weight gain commonly associated with some of the other treatments for type 2 diabetes [[Stonehouse](#), 2012].

Albiglutide is a novel analogue of GLP-1 generated through a genetic fusion of 2 modified recombinant human GLP-1 molecules linked in tandem to recombinant human albumin. Albiglutide is licensed for the treatment of type 2 diabetes as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies (oral anti-diabetic therapies or basal insulin). It has been granted marketing authorisation by the European Medicines Agency (EMA) (March 2014) and the FDA (April 2014). Details of the clinical trial results can be found in the Investigator Brochure (IB).

## 1.2. Rationale

The FDA has issued guidance on evaluating cardiovascular risk in new anti-diabetic therapies to treat type 2 diabetes [FDA [Guidance for Industry](#), 2008]. For a premarketing application that contains a meta-analysis of MACE, for which the upper bound of the 95 percent confidence interval for the relative risk is between 1.3 and 1.8, a post-marketing trial may be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3.

The MACE + meta-analysis of the albiglutide Phase III program (primary endpoint cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina), whilst ruling out an upper bound of the confidence interval for cardiovascular events of 1.8, was not able to rule out (due to a relatively small number of events) a RR upper bound of 1.3. For this reason GSK will conduct this cardiovascular outcome study as a US post-marketing requirement, to evaluate the effect of albiglutide on cardiovascular events in subjects with type 2 diabetes.

Preclinical studies have provided evidence that GLP-1 receptor stimulation favourably effects endothelial function, recovery from ischemic injury, and myocardial function in animals [reviewed in [Okerson](#), 2012]. Albiglutide reduced infarct size assessed 24 hours after 30 minutes temporary left anterior descending coronary artery occlusion in normoglycaemic rats [[Bao](#), 2011]. GLP-1 infusion has been shown to improve endothelial function in subjects with stable coronary disease [[Nystrom](#), 2004]. In subjects with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, the GLP-1 receptor agonist, exenatide, administered at the time of reperfusion has been reported to increase myocardial salvage [[Lønborg](#), 2012]. In the Phase III studies, small mean increases in heart rate (1 to 2 bpm) and a higher incidence of atrial fibrillation/flutter events were observed with albiglutide. It is difficult to predict whether these preclinical and clinical findings will translate into effect on major cardiovascular events.

## 2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b>	
To determine whether albiglutide is non-inferior with respect to MACE when added to glycaemic standard of care versus standard of care alone	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke) [Non-inferiority]</li> </ul>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE [Superiority]<sup>(1 see footnote)</sup></li> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start <sup>(1 see footnote)</sup></li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li>The proportion of subjects achieving glycaemic control (HbA1c ≤ 7.0% at final assessment) with no severe hypoglycaemic incidents and weight gain &lt;5% of body weight <sup>(1 see footnote)</sup></li> <li>The time to first occurrence of a clinically important microvascular event (see Section 6.2.4)</li> <li>Change in HbA1c</li> <li>Change in body weight</li> <li>Patient reported outcomes from TRIM-D/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>All cause mortality</li> <li>Non-fatal SAEs</li> <li>AEs leading to discontinuation of investigational product</li> <li>AE of special interest (see Section 6.2.3)</li> <li>Change in eGFR calculated using MDRD formula</li> <li>Change in blood pressure and heart rate</li> </ul>
<b>Exploratory</b>	
To evaluate patient reported experience of diabetes treatment	<ul style="list-style-type: none"> <li>Patient reported outcomes from study specific questionnaire</li> </ul>
To evaluate (at a subset of sites) barriers to using the electronic health record (EHR) to facilitate trial enrolment and the quality of EHR data for use in populating baseline characteristics and identifying events of interest during trial follow-up. <sup>2</sup>	<ul style="list-style-type: none"> <li>Workflow impact of an EHR-generated list of subjects to facilitate trial enrolment.</li> <li>Concordance, sensitivity, specificity, and accuracy of baseline characteristics extracted from the EHR compared with those reported on the electronic case report form (eCRF)<sup>3</sup></li> <li>Concordance, sensitivity, specificity, and accuracy of EHR-identified events compared with study events <sup>3,4</sup></li> </ul>

1. If the primary endpoint meets the criteria for non-inferiority, a multiple comparisons adjustment strategy will be performed for these 3 secondary endpoints as specified in the Section 8.3.5.
2. Details are provided in a separate EHR ancillary study protocol (Appendix 7). Results from this exploratory investigation will be reported separately from the main clinical study report.
3. Comparison of EHR identified events with study events will be conducted in the same data subset.
4. Analyses to be undertaken after the main trial results are published.

### 3. STUDY DESIGN

#### 3.1. Overall Design

This is a randomised, double blind, parallel-group, placebo-controlled, multicentre study. In countries where marketing authorization has been granted to albiglutide for the treatment of type 2 diabetes it is classified as a Phase IV study, elsewhere it should be considered to be a Phase III study. This study will recruit approximately 9400 subjects with type 2 diabetes and a previous history of cardiovascular disease who are failing to achieve optimal glycaemic control on their current anti-hyperglycaemic regimen. Subjects will be randomised in a 1:1 ratio to albiglutide or albiglutide matching placebo administered once weekly by subcutaneous (s.c.) injection.

All subjects will receive standard of care which can be adjusted by their usual care provider(s) during the study according to clinical need (See Section 3.2). The study comparison is between albiglutide added to standard of care and standard of care alone.

The starting dose of albiglutide will be 30 mg once weekly. If at any stage after 5 weeks of treatment the subject needs to have intensified therapy to improve glycaemic control, the dose of investigational product should be increased before altering the doses of or adding other glucose-lowering medication. This treatment decision will be the responsibility of the investigator. In this case the subject will be called in for an unscheduled visit to increase the dose from 30 mg to 50mg. Subjects randomly assigned to albiglutide matching placebo will also go through the increased dose procedure to maintain study blind. If a subject experiences tolerability issues with the higher, 50mg dose then the investigator may decrease the dose back to 30 mg without the need for an unscheduled visit to supervise down titration. Use of GLP-1 receptor agonists will be prohibited but other glucose-lowering medications permitted, provided they are not contraindicated for the individual subject concerned.

This study is designed with minimal intervention above normal clinical care of subjects with type 2 diabetes, whilst allowing thorough evaluation of cardiovascular and other events of special interest (Section 6.2.3), thus investigating the safety of albiglutide in the typical clinical situation. Sites will employ pre-screening to assess potential subjects for study entry. Screening and randomisation can then occur at the same visit or in close proximity depending on scheduling. Contact with subjects will be every four months after the randomisation visit. HbA1c will be measured at 4 month clinic visits. Serum creatinine and liver function tests (LFTs) will be measured and a targeted physical assessment performed at 8 month clinic visits (Table 1).

The study will be event driven, i.e., follow up will continue until it is projected that approximately 611 adjudicated MACE events will have occurred. Consequently, the maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate, and is estimated to be between 3 and 5 years. If the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years, respectively.

An Executive Committee will be the main decision-making body for the study, in collaboration with the Sponsor (GSK). It is charged with the overall scientific, professional and operational conduct of the study. Amongst other roles pre-specified in its Charter, the Executive Committee will ensure proper study conduct and conformance to the protocol, consider and agree changes to the protocol based on emerging scientific and/or clinical advances (e.g., new emerging data with other GLP-1 receptor agonists), advise on the selection of study sites and assist in subject recruitment strategies.

An IDMC will have study oversight to ensure participant safety and scientific integrity of the data (Section 9.8), an independent Cardiovascular Endpoint Committee (CEC) blinded to treatment allocation will adjudicate cardiovascular outcome events (Section 6.2.1) and a Pancreatitis Adjudication Committee will adjudicate potential events of pancreatitis.

Subject completion is defined as completion of all periods of the study up to and including any follow-up period.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 1), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

### **3.2. Standard of Care**

Anti-hyperglycaemic and cardiovascular medications will be used at the discretion of the usual care provider(s) (or investigator if also the usual care provider), who will be informed of the patient's enrolment in the trial, the use of blinded trial medication, and that use of GLP-1 receptor agonists (other than the use of randomised albiglutide) is contraindicated during the trial period. Usual care providers will be encouraged to follow the most up to date guidelines for diabetes and cardiovascular care based upon local and institutional practice patterns and any relevant published practice guidelines (e.g., Inzucchi, 2012). Treatment for type 2 diabetes will be captured by name and total daily dose at the time of study visits, while other relevant (cardiovascular) concomitant medications will be collected only as drug classes (see Section 5.6.1).

During the study investigators are expected to monitor patients' type 2 diabetes regimens and communicate with usual care providers, who will be responsible for adjusting their regimen in order to achieve locally-appropriate HbA1c goals. The Executive Committee and National Country Leaders will encourage investigators to follow clinical care practice guidelines published by national and international societies regarding type 2 diabetes over the course of the trial. These practice guideline goals will be individualized, with the understanding that currently applicable glycaemic guidelines may vary among different geographic regions. With adherence to local custom and laws



(including privacy regulations such as the Health Insurance Portability and Accountability Act), types of communication may be informal e.g. email or telephone exchanges, to enhance frequency and ease of two-way communication.

Any agent, with the exception of GLP-1 receptor agonists, is acceptable for reaching HbA1c goals. If HbA1c goals are not met following adjustment with oral medications in patients not receiving insulin, an insulin regimen may be initiated. Patients already receiving insulin therapy may up-titrate insulin during the trial if necessary. Patients should be reminded to keep taking their blinded trial medication throughout the course of the trial even in the case after initiation of insulin.

The Executive Committee and National Country Leaders will also monitor the standard of care of management of diabetes and cardiovascular disease. Similar to the management of type 2 diabetes, sites and investigators will be expected to adhere to local clinical practice guidelines. Sites will be provided training on clinical management guidelines to re-enforce standard of care adherence. Information on medications important to management of cardiovascular risk will be captured during study visits. The Executive Committee and National Country Leaders will review on a periodic basis the use of medications for cardiovascular risk prevention to ensure patients are receiving standard of care. If there are unusually low goal attainments for standard of care, site investigators will be advised accordingly.

### **3.3. Discussion of Design**

This study is a clinical outcomes trial required by FDA as a post-marketing requirement to evaluate cardiovascular safety. It will provide important information regarding the cardiovascular safety and metabolic effects of albiglutide treatment of subjects with type 2 diabetes. Sufficient MACE events must be observed during the study to permit the assessment of cardiovascular safety. Consequently, to enter the study subjects must have established cardiovascular disease as well as type 2 diabetes. The study is powered on a predefined number of clinical events, consequently the number of subjects required and study duration may vary from that stated in the protocol.

This will be a double-blind, placebo-controlled study. All subjects will receive placebo or albiglutide in addition to usual standard of care for type 2 diabetes and cardiovascular disease, in order to assess the effect of albiglutide above that of currently available therapies alone.

The primary cardiovascular comparison will be to assess whether albiglutide is non-inferior to placebo with respect to time to first MACE. Missing data may inappropriately bias comparison towards declaring non-inferiority. The longer the duration of a study, the more difficult it is to avoid loss to follow-up and other sources of missing data. The product of the projected duration of this study and the number of subjects to be studied is intended to minimize the risk of missing data whilst still permitting the assessment of the safety of albiglutide to be over an appreciable period of time. Every effort will be made to keep subjects on their assigned study medication according to the protocol. Subjects who stop study medication will be followed throughout the whole study duration. More details about procedures for subject follow-up are provided in Section 4.5.



Phase III studies confirmed the glycaemic efficacy of both 30 mg and 50 mg doses of albiglutide, and both were generally well-tolerated. Although the 30 mg dose was effective at controlling glycaemia for at least 2 years in many subjects with type 2 diabetes, an increase in dose to 50 mg weekly offered additional benefit without significant safety issues (See IB for further details).

### **3.4. Benefit:Risk Assessment**

Albiglutide has been evaluated in an international programme of studies involving approximately 9000 subject-years of overall exposure to date (including over 4000 subject-years of exposure to albiglutide). The programme included 8 well-controlled Phase III studies (including one in subjects with concurrent renal impairment), ranging in duration from 32 weeks to 3 years, and using both 30 mg and 50 mg once weekly dosing. This has permitted a thorough assessment of efficacy, safety, and tolerability in a population of subjects with type 2 diabetes that spanned newly diagnosed individuals treated with diet and exercise alone through to subjects on background oral monotherapy, oral dual therapy, oral triple therapy, and basal insulin.

Summaries of findings from both clinical and non-clinical studies conducted with albiglutide can be found in the IB and in the product labelling for those countries where marketing authorisation has been granted. The following section outlines the risk assessment and mitigation strategy for this protocol:

#### **3.4.1. Risk Assessment**

The identified and potential risks associated with the use of albiglutide, or the GLP-1 receptor agonist class, as well as the mitigation strategy for key risks of clinical significance are provided below. Please refer to the IB for a thorough summary of the nonclinical and clinical experience with albiglutide as well as the complete Guidance for the Investigator. The risks associated with study comparator, placebo, are also provided below. Subjects will have the AE profile of GLP-1 receptor agonists, and albiglutide in particular, explained to them by the investigator and via the informed consent form.

##### **3.4.1.1. Identified Risks**

**Pancreatitis.** Acute pancreatitis has been reported in association with albiglutide and other GLP-1 receptor agonists in clinical trials and during postmarketing experience. Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether they are at increased risk for pancreatitis. Subjects with a history of pancreatitis or who are considered at significant risk of developing pancreatitis are excluded from entering the study. Subjects will be informed of the characteristic symptom of pancreatitis: persistent severe abdominal pain. If pancreatitis is suspected, investigational product should be promptly discontinued and if pancreatitis is confirmed, investigational product will not be restarted.

**Gastrointestinal events.** Albiglutide has not been studied in subjects with severe gastrointestinal (GI) disease, including severe gastroparesis. Subjects with severe gastroparesis will be excluded from the study. Use of albiglutide and other GLP-1

receptor agonists can be associated with GI side effects such as diarrhoea, nausea, and vomiting; the frequency of these events increased as renal function decreased. These types of GI reactions can be associated with dehydration and worsened renal function. (see below and see Section 4.4.4). Other GI related adverse reactions with albiglutide include dyspepsia, gastro-oesophageal reflux disease and constipation.

**Hypoglycaemia.** Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycaemia. However, when used in combination with insulin (or insulin secretagogues) the risk of hypoglycaemia is increased. Investigators will be reminded that it may be necessary to reduce the dose of insulin or insulin secretagogues when starting study medication to reduce the risk of hypoglycaemia. Routine standard of care for subjects treated with insulin secretagogues and insulin includes advice about avoidance of hypoglycaemia which will be reinforced. All subjects are required to have a last indicator of glycemic control of above HbA1c = 7% which is expected to reduce the risk of hypoglycaemia when starting albiglutide.

**Immunogenicity.** Hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III programme. In the Phase III programme one subject (anti-albiglutide antibody negative) developed rash, itching and dyspnoea. Subjects with known allergy to any GLP-1 receptor agonist or excipients of albiglutide are excluded from the study. Subjects will be informed of the symptoms of severe hypersensitivity or allergy and be advised to seek medical assistance immediately. In the Phase III programme approximately 5% of subjects developed anti-albiglutide antibodies. Subjects who tested positive for anti-albiglutide antibodies experienced a similar glycaemic response (HbA1c and fasting plasma glucose) to those who did not test positive for antibodies. Other than injection site reactions (see below), the overall safety profile appeared similar among the subset of subjects who did and those who did not test positive for anti-albiglutide antibodies. Anti-albiglutide antibody formation is not expected to impact the overall safety of albiglutide treatment and therefore will not be measured routinely in this study.

**Injection site reactions.** Albiglutide injections may cause rash, erythema or itching and/or other reactions at the site of injection. Subjects will be advised that when injecting in the same region, to use a different injection site each week. In the Phase III program, most subjects with injection site reactions did not test positive for anti-albiglutide antibodies. However, injection site reactions were reported more frequently among those who did test positive for anti-albiglutide antibodies (41% of the antidrug antibody positive subjects reported one or more injection site reactions) than among those who were consistently antibody negative (14% of the antidrug antibody negative subjects reported one or more injection site reactions).

**Other adverse reactions** (e.g. pneumonia, atrial fibrillation/flutter, and appendicitis). In the Phase III programme in type 2 diabetes, other possible albiglutide related adverse reactions were identified. These events occurred at a cumulative incidence <3% in studies up to 3 years in duration. These events were reported more frequently with albiglutide than comparators.

### 3.4.1.2. Potential Risks

**Thyroid C-cell tumours.** GLP-1 receptor agonists, including albiglutide increase serum calcitonin in rodents and other GLP-1 receptor agonists are associated with thyroid C-cell focal hyperplasia and C-cell tumours in rodents. It is unknown whether GLP-1 receptor agonists are associated with thyroid C-cell tumours in humans, including medullary thyroid cancer (MTC). Subjects with a personal or family history of MTC or subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) are excluded from the study. Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. Routine monitoring of serum calcitonin is not recommended. However, if serum calcitonin is found to be elevated the subject should be referred to a specialist for further evaluation. If MTC or other thyroid C-cell neoplasia is diagnosed, investigational product will be discontinued.

**Other malignant neoplasms** Concerns have been raised regarding use of incretin based therapies and other malignancies such as pancreatic cancer [[Egan, 2014](#)], malignancy when used in combination with insulin based on hypotheses of biological plausibility [[European Public Assessment Report, 2014](#)], and haematological malignancies [[FDA Summary Basis of Approval, 2014](#)].

**Hepatotoxicity.** Hepatotoxicity is an area of interest in drug development. Patients with type 2 diabetes are at increased risk for liver enzyme abnormalities and disease related liver conditions. One subject treated with albiglutide in the Phase III clinical programme developed probable drug induced liver injury with an asymptomatic elevation in alanine amino transferase (ALT) and total bilirubin although the cases had some atypical features and complicating factors. Routine liver safety laboratory evaluations will be conducted and specific withdrawal criteria for elevated liver function tests have been defined (See Section [4.4.3](#)).

**Subject population with severe renal impairment (eGFR <30 mL/min/1.73m<sup>2</sup>).** Experience in type 2 diabetes subjects with severe renal impairment is limited (in the Phase III programme a total of 19 subjects with eGFR <30 mL/min/1.73m<sup>2</sup> received albiglutide).

In a Phase 3 study of patients with varying degrees of renal impairment, in the albiglutide group, on-therapy GI AEs occurred with a higher incidence and higher event rate in subjects with moderate and severe renal impairment compared to those with mild renal impairment. Because these GI events may lead to dehydration and worsen renal function, worsening renal function will be closely evaluated as an AE of special interest, serum creatinine will be measured every 8 months, and subjects will discontinue IP if eGFR falls below 15 mL/min/1.73m<sup>2</sup>. Subjects with known severe renal impairment are excluded from the study (see Section [4.4.4](#)).

**Drug Interactions.** Like other members of the class, albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the development programme, drug interactions studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant PK or PD effects. Investigators will be advised

to take the effect of albiglutide on gastric emptying into account when prescribing concomitant medication.

**Pregnancy and Lactation.** Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. It is not known if albiglutide is secreted into human milk during lactation. Given that albiglutide is an albumin-based protein therapeutic, it is likely to be present in human milk. Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation. Subjects who are breastfeeding, pregnant or planning a pregnancy during the course of the study are excluded. Additionally, all females of child-bearing potential must be taking adequate contraception during the study and have a negative pregnancy test prior to entry.

**Placebo control.** In subjects treated with placebo, symptoms and long-term risks of hyperglycaemia may not improve or may worsen. During the study, intensification of glucose-lowering treatments other than study drug will be allowed in both treatment arms with a treat-to-target approach. Albiglutide placebo injections may cause injection site reactions. Subjects will be advised when injecting into the same region to use a different injection site each week.

### 3.4.2. Benefit Assessment

In subjects with type 2 diabetes albiglutide treatment resulted in clinically relevant lowering of HbA1c at both the 30 mg and 50 mg doses when given as monotherapy and in combination with metformin, sulfonylureas (SUs), thiazolidinedione or basal insulin. The durability of the effect on glycaemic control was shown over a study period of up to 3 years. Consistent with its mechanism of action, albiglutide was not associated with clinically relevant hypoglycaemia except when used in combination with an SU or insulin, and incidence rates with the combination were less than those reported with SUs or insulin alone. Treatment with albiglutide generally produced a steady reduction in weight over time.

For subjects not yet on insulin at the start of the study, data from the Phase III programme suggest that the use of albiglutide once weekly in a pen device may have the potential to delay the need to start daily insulin injections. This will be formally assessed within this trial. Similarly, it is possible that for those already taking basal insulin, albiglutide may delay the need to introduce short-acting prandial injections and for those taking basal/bolus or pre-mixed insulin, it may reduce the dosage of insulin and/or the number of daily injections needed to achieve good glycaemic control. These will also be evaluated in the study.

Subjects in the placebo arm will also be receiving effective anti-hyperglycaemic medication which will be titrated up or down as required to improve or maintain glycaemic control, and therefore these subjects should also demonstrate reductions in HbA1c, though weight gain (rather than weight loss) may occur depending upon the medication selected.

Finally, as a result of participating in a clinical trial, each subject will receive more contact with the study site than would be performed as part of their usual standard of care.

### **3.4.3. Overall Benefit:Risk Conclusion**

Taking into account the measures taken to minimise risk to subjects participating in this study, the known and potential risks identified with albiglutide are justified by the benefits have been demonstrated in subjects with type 2 diabetes.

## **4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA**

### **4.1. Inclusion Criteria**

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB for albiglutide and in the product label for those countries where marketing authorisation has been granted.

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

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

1. Men or women at least 40 years old with a diagnosis of type 2 diabetes.
2. Established cardiovascular disease, including at least 1 of the following:
  - a. Coronary artery disease with EITHER of the following:
    - Documented history of spontaneous myocardial infarction, at least 30 days prior to Screening.
    - Documented coronary artery disease (CAD)  $\geq$  50% stenosis in 1 or more major epicardial coronary arteries, determined by invasive angiography, or history of surgical or percutaneous (balloon and/or stent) coronary revascularization procedure (at least 30 days prior to Screening for percutaneous procedures and at least 5 years prior to Screening for coronary artery bypass graft (CABG)).
  - b. Cerebrovascular disease – ANY of the following:
    - Documented history of ischaemic stroke, at least 90 days prior to study entry.
    - Carotid arterial disease with  $\geq$  50% stenosis documented by carotid ultrasound, magnetic resonance imaging or angiography, with or without symptoms of neurologic deficit.

- Carotid vascular procedure (e.g. stenting or surgical revascularisation), at least 30 days prior to Screening.
- c. Peripheral arterial disease (PAD) with EITHER of the following:
- intermittent claudication and ankle:brachial index < 0.9 in at least one ankle
  - prior non-traumatic amputation, or peripheral vascular procedure (e.g. stenting or surgical revascularisation), due to peripheral arterial ischaemia.
3. HbA1c >7.0% (53 mmol/mol) based on the most recent documented laboratory assessment measured no more than 6 months prior to randomization. Local laboratory HbA1c values taken as part of usual care are permitted.
4. Female: subject is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test for females of reproductive potential only), not breastfeeding, and at least one of the following conditions applies:
- a. Reproductive potential and agrees to follow one of the options listed in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (e.g. combined oral contraceptive pill; see [Appendix 2](#)) from 30 days prior to the first dose of study medication and until after the last dose of study medication and completion of the follow-up visit.
- This does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent. Other situations in which contraception in FRP may not need to be mandated should be discussed with the Medical Monitor.
- b. Non-reproductive potential defined as either:
- Pre-menopausal with one of the following: (i) documented tubal ligation; (ii) documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion; (iii) hysterectomy; or (iv) documented bilateral oophorectomy, or;
  - Postmenopausal defined as 12 months of spontaneous amenorrhea and age appropriate (i.e. >50 years). In questionable cases, a blood sample with simultaneous follicle stimulating hormone (FSH) >40 mIU/mL and oestradiol <40 pg/mL (<140 pmol/L) is confirmatory, depending on local laboratory ranges. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.
5. Able and willing to provide informed consent.

## 4.2. Exclusion Criteria

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

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

1. eGFR calculated using MDRD formula  $<30\text{mL}/\text{min}/1.73\text{m}^2$  (based on the most recent documented serum creatinine laboratory assessment measured no more than 6 months prior to randomization. Local laboratory creatinine values taken as part of usual care are permitted) or renal replacement therapy.
2. Use of a GLP-1 receptor agonist at Screening.
3. Severe gastroparesis requiring therapy within 6 months prior to Screening.
4. History of pancreatitis or considered clinically at significant risk of developing pancreatitis during the course of the study (e.g. due to symptomatic gallstones, excess alcohol use).
5. Personal or family history of medullary carcinoma of the thyroid or subject with MEN-2. Personal history of pancreatic neuroendocrine tumours. In the opinion of the investigator, the subject has a medical history which might affect his / her ability to remain in the study for its entire duration, or which might limit management, such as life expectancy of  $<5$  years (e.g. due to active malignancy).
6. Subject has a medical history which in the opinion of the investigator might limit the individual's ability to take trial treatments for the duration of the study or to otherwise complete the study.
7. Breastfeeding, pregnancy, or planning a pregnancy during the course of the study. Pregnancy test will be required in women of child bearing potential. Women who have undergone a sterilisation procedure or who are clearly post-menopausal will not be required to undergo pregnancy testing. Women who have developed spontaneous secondary amenorrhoea of 12 months or more where post-menopausal status is in doubt, a blood sample where FSH  $>40\text{MU}/\text{mL}$  and oestradiol  $<40\text{ pg}/\text{mL}$  ( $<140\text{ pmol}/\text{L}$ ) are simultaneously measured will be considered confirmatory.
8. Known allergy to any GLP-1 receptor agonist or excipients of albiglutide.
9. Use of another investigational product within 30 days or according to local regulations, or currently enrolled in a study of an investigational device.
10. Any other reason the investigator deems the subject to be unsuitable for the study.

### **4.3. Screening/Baseline Failures**

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements [Schulz, 2010], and respond to queries from regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any SAEs.

Re-screening of subjects who did not meet the eligibility criteria for HbA1c or creatinine based on local laboratory values taken as part of usual care is permitted. If values were based on laboratory results as part of usual care then one re-test is permitted within the protocol at Screening. Any future re-screening will be based on laboratory results obtained as part of usual care.

### **4.4. Criteria for Early Discontinuation of Investigational Product**

The primary analysis will be conducted on an ITT analysis basis so it is important that every subject is followed for the duration of the study, regardless of whether the subject continues to take investigational product, unless consent for all follow up is actively withdrawn.

The requirements for handling early discontinuations from investigational product are described below. Details of the requirements for subject follow-up are provided in Section 4.5.

#### **4.4.1. Early Discontinuation of Investigational Product**

If a subject chooses to discontinue investigational product between scheduled face-to-face visits they should be encouraged to contact the investigator site by telephone. Subjects should first be counselled to consider temporary discontinuation of investigational product prior to choosing to discontinue investigational product permanently, unless the reason for discontinuation is one of those listed below (Reasons for Discontinuation of Investigational Product). If the discontinuation is permanent, the subject should be asked to attend the clinic as soon as possible to complete the assessments as for the final study visit (see Table 1) and then continue in the study for follow-up. The procedures for follow-up for a subject who permanently discontinues treatment with investigational product prior to the study end are given in Section 4.5.

In all cases, reasons for discontinuation of investigational product and the date of last dose will be recorded.



#### 4.4.2. Reasons for Discontinuation of Investigational Product

Any subject experiencing the following will be required to discontinue investigational product:

- AE:
  - Pancreatitis, acute or chronic.
  - Pancreatic cancer.
  - MTC or other thyroid C-cell neoplasia. In subjects where a treatment emergent thyroid nodule is identified, if serum calcitonin is measured at the discretion of the Investigator (e.g., per local guidelines) and found to be >100 ng/L this should prompt further investigation for MTC and potential interruption or discontinuation of investigational product until diagnosis has been resolved.
  - Liver chemistry abnormalities exceeding the threshold criteria outlined in Section 4.4.3
  - Severe allergic/hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology.
  - Other AE which, in the opinion of the investigator precludes continuation of dosing.
- eGFR<15ml/min/1.73m<sup>2</sup> (Section 4.4.4) or the need for renal replacement therapy.
- Subject becomes pregnant during the study.
- Need for chronic use of a prohibited concomitant medication (Section 5.6.2)
- Decision by subject or proxy.
- Sponsor terminated study.
- Investigator site closed and subject was unable to transfer to another investigative site.

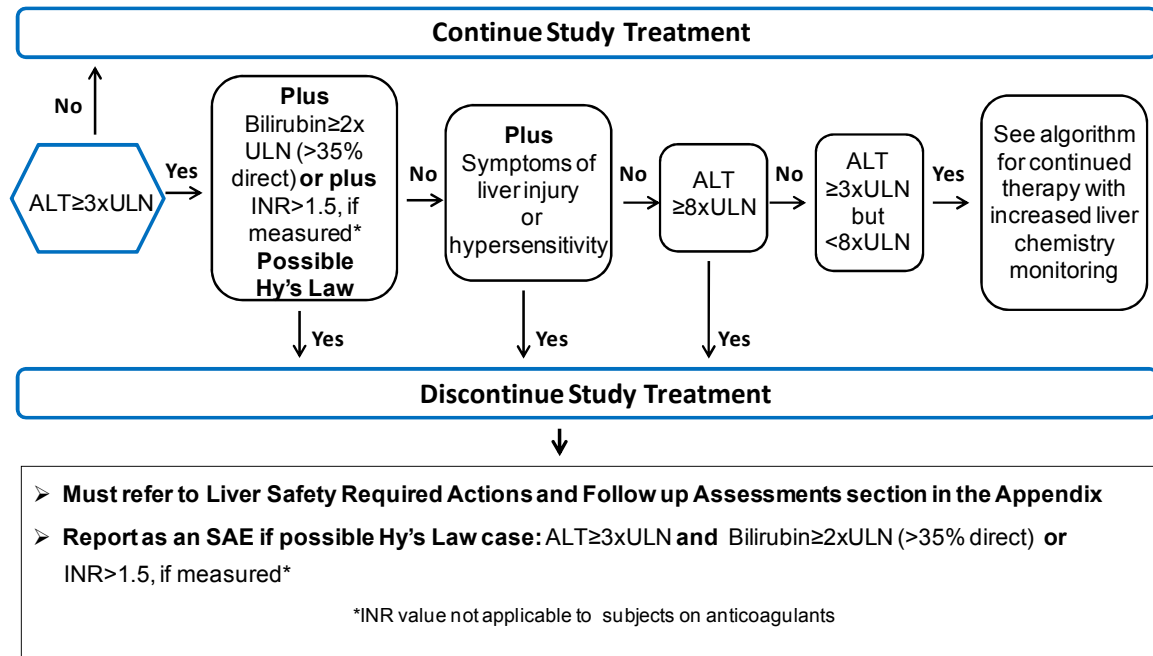
If investigational product is discontinued, the subject should continue in the study and be followed until the final study visit as detailed in Section 4.5.

#### 4.4.3. Liver Chemistry Stopping Criteria

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

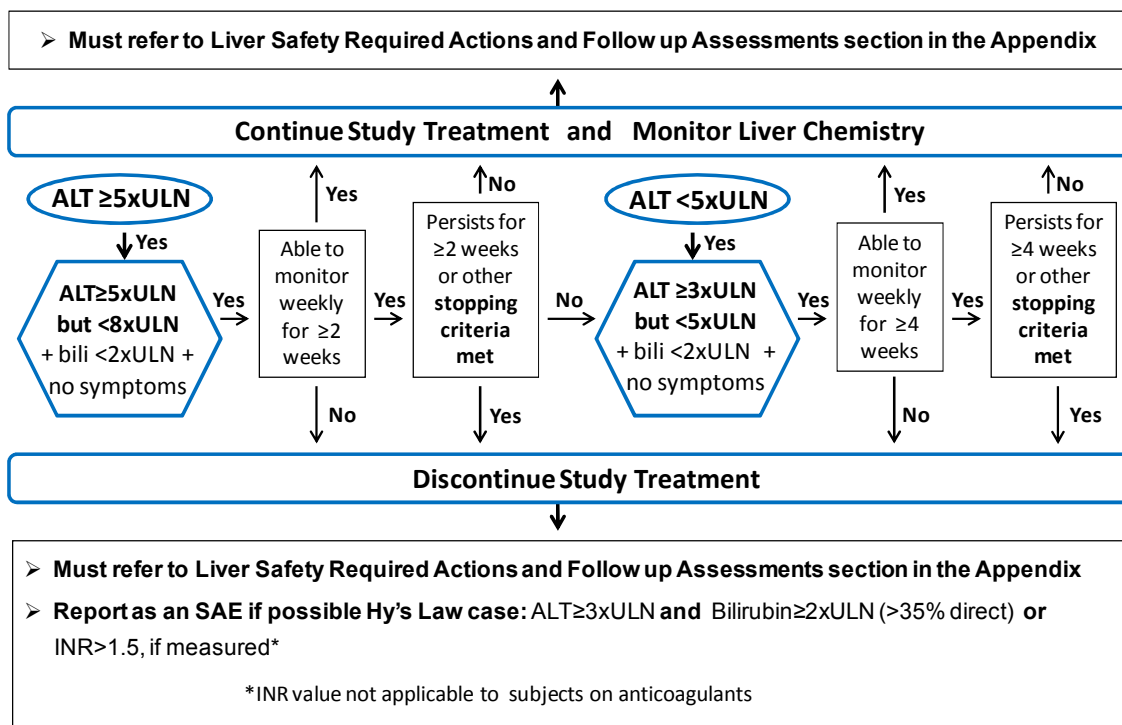
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

### Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver safety required actions and follow up assessments section can be found in [Appendix 3](#).

### Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3xULN$ but $< 8xULN$



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 3](#).

Drug re-challenge following drug induced liver injury is not allowed.

Restart may be considered if GSK Medical Governance approval is granted (see [Appendix 4](#) for details). Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with human leukocyte antigen (HLA) markers of liver injury.

#### 4.4.4. eGFR Stopping Criteria

A baseline eGFR  $\geq 30\text{mL/min/1.73m}^2$  is a requirement for entering the study. Subjects can continue to take investigational product if functioning well as long as eGFR is  $\geq 15\text{mL/min/1.73m}^2$ .

During this study, if a subject's eGFR approaches  $30\text{mL/min/1.73m}^2$  closer monitoring of renal function is considered prudent, according to standard clinical practice. Particular

care should be taken to monitor renal function in subjects with renal impairment reporting severe adverse GI events. If eGFR is  $<15\text{mL}/\text{min}/1.73\text{m}^2$  and considered irreversible based on consecutive measurements the investigational product should be discontinued, the subject continue in the study and be followed until the final study visit.

If eGFR is  $<15\text{mL}/\text{min}/1.73\text{m}^2$  and the patient is considered to have temporary acute kidney injury that is potentially reversible, the investigational product should be temporarily discontinued until the eGFR is stable and  $\geq 15\text{mL}/\text{min}/1.73\text{m}^2$ . Events considered to reflect worsening renal function should be reported as SAE/AEs and targeted eCRFs completed for this AE of special interest (Section 6.2.3).

#### **4.5. Procedures for Subject Follow-up**

As described in Section 4.4, subjects who permanently discontinue investigational product will be asked to attend the clinic as soon as possible. They will continue in the study for follow-up. Five weeks ( $\pm 1$  week) after discontinuation of investigational product, subjects will be contacted for a follow-up by telephone. They will be asked to return to clinic according to the 8 monthly visit schedule and in addition be contacted by telephone at a time corresponding to the 4-monthly visit they would have otherwise made to replenish study medication supply. If instead of these interim telephone contacts the subject prefers to attend clinic every 4 months as originally scheduled that is an acceptable alternative.

If a subject permanently discontinues investigational product and is unable to attend visits in-person, he/she will be contacted by telephone or other methods to assess study outcomes and vital status, unless the subject has specifically withdrawn consent for all forms of contact. Follow-up of subjects who withdraw consent for contact is described below.

Every effort should be made to educate the subjects on the importance of remaining in the study and attending scheduled study visits including those required after early discontinuation of investigational product.

Other subject follow-up options to collect study outcomes and vital status should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes and vital status is acceptable to the subject, then the subject will be deemed not to have withdrawn consent for follow-up.

##### **4.5.1. Withdrawal of Consent for Contact**

Subjects who no longer wish to attend study visits in-person will be asked to be contacted by telephone or other methods to assess study outcomes and vital status. However, if a subject specifically withdraws consent to be contacted for additional information, no further study visits or study-related telephone contacts can be conducted. Information regarding study outcomes or vital status will continue to be collected from available sources including those in the public domain. Additionally, alternative permitted options to obtain study outcomes and vital status will be reviewed based on accepted local laws and regulations. For any subject who withdraws consent for contact, the study site will be

asked to document the discussion with the subject regarding each of the contact options that were offered.

#### **4.5.2. Subjects Deemed Lost to Follow-up**

Finally, investigators should make every effort to contact subjects who are deemed lost to follow-up and who have not withdrawn consent to follow-up contacts, including pursuing any alternative contact methods permitted by local regulations. Where permitted, a third party may be used to locate alternative subject contact information that will be provided to the investigator. All attempts to contact subjects will be documented in the subject's eCRF and source notes.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject. Should the subject continue to be unreachable, then and only then will he/she be considered "Lost to Follow-up". Nonetheless, efforts to attempt to locate and contact the subject will continue until the study end.

## **5. STUDY TREATMENTS**

### **5.1. Investigational Product and Other Study Treatment**

Albiglutide (and albiglutide matching placebo) will be provided as a fixed-dose, fully disposable pen injector system for delivery of the investigational product (albiglutide or albiglutide matching placebo) from a prefilled dual chamber glass cartridge that is an integral part of the pen. The pen is intended for single use by the subject. It is designed for manual reconstitution of the dose, priming and insertion of the pen needle, and manual injection by the subject.

Albiglutide (or albiglutide matching placebo) is intended for self-administration as a subcutaneous injection in the abdomen, thigh or upper arm region. Rotation of use of injection sites is recommended. Albiglutide and insulin may be injected in the same body region but the injections should not be adjacent to each other. The albiglutide pen includes a mechanical locking system that prevents the user from manipulating the dose button before the cartridge has been fully reconstituted. Reconstitution is performed through rotation of the pen housing parts. The pen is designed to work with standard pen needles.

When the injector pen product is reconstituted by the subject, a neutral, isotonic solution is produced. Separate pens are required to deliver either 30 mg of albiglutide, 50 mg of albiglutide, or matching placebo in a 0.5-mL injection volume.

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

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

The investigational product (albiglutide and albiglutide matching placebo) must be stored in a secure area at 2°C to 8°C and protected from freezing. Each site must maintain a temperature log. Access to and administration of the investigational product will be limited to the investigator and authorised site staff (investigator or designee). Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Procedures for the disposal of unused study treatment will be provided in the SRM.

Investigational product (albiglutide or albiglutide matching placebo) will be administered once weekly by subcutaneous injection. The first dose is to be administered at the clinic. The starting dose of albiglutide will be 30 mg once weekly. If at any stage after 5 weeks of treatment in the opinion of the investigator the subject needs to have intensified therapy to improve glycaemic control, the dose of investigational product should be increased before altering the doses of other glucose-lowering medication. In this case the subject will be called in for an unscheduled visit to supervise an increase in dose from 30 mg to 50 mg. Subjects randomly assigned to albiglutide matching placebo will also go through the increased dose procedure to maintain study blind. If a subject experiences tolerability issues with the higher, 50mg dose then the investigator may decrease the dose back to 30 mg without the need for an unscheduled visit to supervise down titration, other than for the subject to collect pens of the correct dose.

Albiglutide (or albiglutide matching placebo) may be administered at any time of day without regard to meals. Preferably, it should be administered once a week on the same day each week. The day of weekly administration can be changed if necessary as long as the last dose was administered 4 or more days previously. If a dose is missed, it should be administered as soon as possible within 3 days after the missed dose. Thereafter, subjects can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, subjects should wait and administer their next regularly scheduled weekly dose.

If a subject misses 4 or more consecutive doses, the investigator should contact the medical monitor to discuss options for helping assure better compliance.

## **5.2. Treatment Assignment**

Subjects will be assigned to study treatment in accordance with the randomisation schedule.

Randomised treatment assignment will be done via the Interactive Voice Response System (IVRS), and randomisation will be implemented based on a sequestered fixed randomisation schedule. Study centre personnel will call the IVRS once a subject has met all prerequisites for randomization; the IVRS will assign treatment.

Blinded study centre personnel will receive a randomisation notification indicating the unique subject identifier (randomisation number) and the date and time of randomisation. Each randomisation number will be a unique identifier. Once a randomisation number has been assigned, the number will not be reused even if the subject withdraws before receiving any investigational product. Details of the treatment assignment process are contained in the SRM.

### 5.3. Blinding

This is a double-blind study, neither the subject nor the study physician will know which of the two treatments (albiglutide or placebo) the subject is receiving.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency or in the event of a serious medical condition, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator**. Investigators have direct access to the subject's individual study treatment. It is preferred (but not mandatory) that the investigator first contacts the GSK Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment. If GSK study personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be fully documented in the appropriate data collection tool.

If a subject is unblinded by the investigator or treating physician then discontinuation of investigational product treatment for that subject will be at the discretion of the investigator. However, the subject should continue to be followed in the study (see Section 4.5).

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

### 5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned unused by study subjects, and the amount received from and returned to GSK,

when applicable. Product accountability records must be maintained throughout the course of the study.

## **5.5. Treatment Compliance**

Subjects will be instructed to return all unused and used injector pens at the visits specified in the Time and Events Table ([Table 1](#)) in order to perform drug accountability and determine compliance. Subjects will be provided with a sharps container for the disposal of used pens. To comply with health and safety considerations there will be no count made of used pens; only returned unused pens will be counted. In addition, subjects will be provided with a pre-printed card at each dispensing visit to record the date of each dose. The card is to be returned at the next dispensing visit with the unused pens.

## **5.6. Concomitant Medications and Non-Drug Therapies**

### **5.6.1. Permitted Medications and Non-Drug Therapies**

The usual care provider will manage the subjects according to standard of care, following local prescribing information. Close adherence to professional society guidelines for standard of care therapies in type 2 diabetes and cardiovascular disease will be emphasized during study conduct. Standard of care is described in greater detail in [Section 3.2](#).

Unless specified as a prohibited medication in [Section 5.6.2](#), all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned.

Like other members of the class, albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. This should be taken into account by investigators when prescribing concomitant medication.

It may be necessary to reduce the dose of concomitantly administered insulin secretagogues (such as SUs) or insulin to reduce the risk of hypoglycaemia when starting albiglutide.

All concomitant anti-hyperglycaemic medications (name of agent, total daily dose, start and stop dates) will be recorded in the eCRF at each visit. Concomitant cardiovascular medications taken during the study will also be recorded at each visit by class of agent. Additionally, all medications used within the 30 days prior to the onset and throughout the duration of an SAE, AE of special interest ([Section 6.2.3](#)), or an AE leading to discontinuation of investigational product will be recorded as individual agents, reason for use, together with start dates (and stop dates if applicable) and any changes since any previous AE.



### **5.6.2. Prohibited Medications and Non-Drug Therapies**

Subjects may not take a GLP-1 receptor agonist (other than blinded investigational product), nor any investigational drug, during the study (and any follow-up period after discontinuing investigational product).

If a subject receives a prohibited medication, a protocol deviation will be recorded.

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

Following the final study visit subjects will be contacted by telephone  $5 \pm 1$  weeks after last dose of study medication to assess any AEs ongoing since the last visit or newly emergent.

Subjects will be treated as deemed appropriate by the investigator following the end of the study. Investigational product will not be provided to subjects by GSK after the end of the study.

The half-life of albiglutide is approximately 5 days, and significant therapeutic concentrations can persist for 3 to 4 weeks after discontinuation. The choice of other medicinal products and dose selection should be considered accordingly, as adverse reactions may continue and efficacy may, at least partly, persist until albiglutide levels decline.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition whether or not GSK is providing specific post study treatment.

### **5.8. Treatment of Study Treatment Overdose**

No data are available with regard to albiglutide overdose in humans. The highest recommended dose of albiglutide is 50 mg once weekly.

During clinical studies of subjects with type 2 diabetes, the highest dose of albiglutide administered was 100 mg subcutaneously every four weeks for 12 weeks. This dose was associated with an increased frequency of nausea, vomiting, and headache.

There is no specific antidote for overdose with albiglutide. In the event of a suspected overdose, the appropriate supportive clinical care should be instituted, as dictated by the subject's clinical status. Anticipated symptoms of an overdose may be severe nausea, vomiting or headache. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the half-life of albiglutide (5 days).

## **6. STUDY ASSESSMENTS AND PROCEDURES**

The schedule of study assessments is shown in [Table 1](#) and [Table 2](#). Detailed procedures for each assessment are provided in the SRM.

**Table 1 Time and Events Table**

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post rand.)	Clinic Visit Month 4 ± 18 days then every 4 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Final study clinic visit <sup>4</sup> (or early withdrawal)	Follow up Phone Call 5 ± 1 weeks after last IP dose
Written informed consent	X						
Review of Inc/excl criteria	X	X					
Demography & directed medical history	X						
Assessment of MACE and micro-vascular events				X		X	
HbA1c	X <sup>5</sup>			X		X	
Serum creatinine (eGFR)	X <sup>5</sup>			X (alternate visits) <sup>2</sup>		X	
Liver Function Tests (LFTs) <sup>6</sup>		X		X (alternate visits) <sup>2</sup>		X	
Record available information on most recent lipid assessment <sup>7</sup>		X		X (annually)		X	
Genetic sampling <sup>8</sup>		X					
Patient reported outcomes questionnaires <sup>9</sup>		X <sup>10</sup>		X (alternate visits) <sup>2</sup>		X	
Key concomitant non-diabetes medication		X		X		X	X
Diabetes medication		X		X		X	X
Study drug reminder			X	X	X		
Physical examination <sup>11</sup>		X		X (alternate visits) <sup>2</sup>		X	
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X	X	X	X
Pregnancy test <sup>12</sup>	X	X					
Study drug dispense/compliance <sup>13</sup>		X		X	X	X	

1. Subjects who discontinue investigational product should be handled as described in Section 4.4 and Section 4.5 and in Table 2.

2. Assessments at month 8, 16, 24 etc. will include patient reported outcomes questionnaires, serum creatinine (eGFR), LFTs and physical examination. Those at months 4, 12, 20 etc do not.

3. Screening and Randomisation can occur at the same visit if all eligibility information is available. If Screening and Randomisation occur at the same visit assessments should not be duplicated.

4. Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.

5. HbA1c and creatinine assessed using local laboratories at Screening visit and measured no more than 6 months prior to randomisation. If HbA1c or creatinine have not been assessed in the previous 6 months assessments to be performed via a central laboratory and results available prior to randomization. The investigator has the discretion to repeat

screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.

6. Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT. Blood samples for LFTs at randomization must be collected prior to the first dose of investigational product.
7. Lipid values (TC, LDLc, HDLc, Tg) to be recorded as available from routine clinical care at baseline and annually thereafter. If results are unavailable, lipids tests are not to be performed for the study.
8. Informed consent for genetic research must be obtained before collecting a sample. This can be collected at any time after genetic consent has been obtained and randomisation has occurred.
9. TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
10. TRIM-D is not required for subjects whose diabetes is treated by diet and exercise alone at Baseline.
11. See Section 6.2.7.
12. Only applies to women of child bearing potential. At screening perform urine pregnancy test. If positive, send serum sample to the central laboratory for confirmation. At Randomisation perform a urine pregnancy test. If result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised. If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. See Section 6.2.6.
13. Study drug dispensing not performed at final visit, compliance check not performed at Randomisation.

**Table 2 Time and Events Table for Subjects Who Permanently Discontinue IP Prior to the End of the Study**

Procedures	Clinic visit as soon after permanent discontinuation of IP as possible	Phone Call 5 ± 1 week after last IP dose	Continue contact schedule established at randomisation 4 monthly ± 1 month. <i>Telephone</i> <sup>1,2</sup>	Continue contact schedule established at randomisation 4 monthly ± 1 month. <i>Clinic visit</i> <sup>1,3</sup>	Final study clinic visit <sup>4</sup>
Assessment of MACE and micro-vascular events	X		X	X	X
HbA1c	X			X	X
Serum creatinine (eGFR)	X			X	X
Liver Function Tests (LFTs) <sup>5</sup>	X			X	X
Record available information on most recent lipid assessment <sup>6</sup>	X		X (annually)	X (annually)	X
Patient reported outcomes questionnaire <sup>7</sup>	X				
Key concomitant non-diabetes medication	X	X	X	X	X
Diabetes medication	X	X	X	X	X
Physical examination <sup>8</sup>	X			X	X
AEs leading to IP discontinuation	X				
SAEs, AEs of special interest,	X	X	X	X	X
Study drug compliance	X				

1. After subjects permanently discontinue IP, follow-up should continue on the 4-monthly schedule established at randomisation.
2. Where a subject would have been scheduled to attend clinic at months 4, 12, 20, 28 etc after randomisation, a telephone contact will be performed instead (with assessments as shown above).
3. Where a subject would have been scheduled to attend clinic at months 8, 16, 24, 32 etc after randomisation, a clinic visit will be performed (with assessments as shown above). If a subject who has permanently discontinued IP is unable to attend clinic then they will be contacted by telephone instead and the telephone contact assessments will be performed.
4. Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.
5. Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT.
6. Lipid values (TC, LDLc, HDLc, Tg) to be recorded as available from routine clinical care annually. If results are unavailable, lipids tests are not to be performed for the study.
7. TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
8. See Section 6.2.7.

## 6.1. Critical Baseline Assessments

Disease, and therapy history, including cardiovascular medical history/risk factors will be assessed at Baseline. Investigators are encouraged to implement lifestyle modifications and adjust or initiate the appropriate pharmacotherapy throughout the study as recommended by current locally followed therapeutic cardiovascular and diabetes guidelines for participants in the study. Screening and randomisation can occur at the same visit depending on availability of information to determine eligibility of the subject to enter the study.

## 6.2. Safety

The following sections provide further detail on the safety assessments. Planned time points for all safety assessments are listed in the Time and Events Table ([Table 1](#)). Unscheduled visits will occur as medically necessary. Detailed procedures for obtaining each assessment are provided in the SRM.

Safety endpoints are described in [Section 2](#) and will include monitoring of cardiovascular events ([Section 6.2.1](#)), deaths, AEs of special interest ([Section 6.2.3](#)), clinically significant microvascular events ([Section 6.2.4](#)), SAEs and AEs leading to discontinuation of investigational product.

Liver chemistry stopping and follow-up criteria and AEs are described in [Section 4.4.3](#) and [Appendix 3](#).

### 6.2.1. Cardiovascular Events

Events referred to the CEC by the investigator as potential endpoints or transient ischemic attacks (TIAs) will not be collected or reported as SAEs, regardless of the adjudication outcome ([Section 6.2.2](#))<sup>1</sup>. These events will be reviewed by an Independent Data Monitoring Committee ([Section 9.8](#)).

The CEC will review and adjudicate the following clinical events:

- Myocardial infarction
- Stroke
- Unstable angina requiring hospitalization
- Hospitalization for heart failure
- Sudden cardiac death
- TIA

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<sup>1</sup> There is one exception to this statement. Per requirement of the Mexican Ministry of Health, all events referred to the CEC by Mexican investigators will also be submitted as SAEs to the Mexican Ministry of Health.

- In addition, all clinical events submitted for adjudication and all other SAEs with a fatal outcome will be reviewed and adjudicated to classify the cause of death as cardiovascular or non-cardiovascular.

When the local investigator reported event and the CEC decision on the nature of the event differ, the CEC's decision will be considered final. The detailed descriptions of the endpoint (and TIA) definitions necessary for adjudication are contained within the CEC Charter (available on request). The guiding principle will be the "2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular and Stroke End Point Events for Clinical Trials" [ACC/AHA, 2014] and the "Third Universal Definition of Myocardial Infarction" endorsed by the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation (WHF) [Thygesen, 2012].

Source documentation required to support the adjudication of the events is described in the SRM. Recording of potential endpoint and TIA events in the eCRF and submission of source documentation will be required for clinical events meeting reporting criteria whether or not an endpoint event is suspected by the investigator.

#### **6.2.1.1. Other CV Events**

GSK has identified other CV events of special interest for all clinical studies. Investigators will be required to fill out event specific data collection tools for the following cardiovascular events which meet SAEs criteria or are non-serious events that result in discontinuation of investigational product:

- Arrhythmias (other than atrial fibrillation/flutter, see Section 6.2.3)
- Valvulopathy
- Pulmonary hypertension
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation (other than urgent revascularisation for unstable angina, a component of a secondary endpoint)

This information should be recorded in the specific cardiovascular eCRF within one week.

#### **6.2.2. Adverse Events (AE) and Serious Adverse Events (SAEs)**

The definitions of an AE or SAE can be found in [Appendix 5](#).

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

For this study events of myocardial infarction, stroke, unstable angina requiring urgent revascularization, hospitalization for heart failure, TIA and sudden cardiac death will not

be collected or reported as AEs or SAEs. These events will be collected separately, subjected to blinded adjudication by an independent CEC using prespecified diagnostic criteria, and reported separately (Section 6.2.1.1). All other events that meet serious criteria as defined in [Appendix 5](#) should be reported as SAEs.

All events with an outcome of death will be adjudicated to classify the cause of death as specifically cardiovascular or non-cardiovascular. Any event resulting in death should be reported as a SAE unless the event is myocardial infarction, stroke, unstable angina w/ urgent revascularization, Heart failure, TIA or sudden cardiac death which the protocol specifies are not to be collected as adverse events.

The study will not collect all non-serious AEs. Non-serious AEs leading to discontinuation of investigational product and non-serious AEs of special interest (see Section 6.2.3) will be collected.

Any events not specifically addressed above should be reported as an AE or SAE according to the definitions in [Appendix 5](#).

#### **6.2.2.1. Time period and Frequency for collecting AE and SAE information**

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 6.2.2.3), at the timepoints specified in the Time and Events Table ([Table 1](#)).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in [Appendix 5](#).
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in [Appendix 5](#).

**6.2.2.2. Method of Detecting AEs and SAEs**

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

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

Additionally subjects will be asked specific questions about the occurrence of AEs of special interest (Section [6.2.3](#)).

**6.2.2.3. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section [6.2.3](#)) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section [4.5](#)). Further information on follow-up procedures is given in [Appendix 5](#).

**6.2.2.4. Sentinel Events**

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/severe neutropenia
- Anaphylaxis and anaphylactoid reactions (see also Section [6.2.3](#))
- Hepatotoxicity (see also Section [6.2.3](#))
- Acute renal failure
- Seizure
- Stevens Johnson syndrome/toxic epidermal necrosis

**6.2.2.5. Regulatory Reporting Requirements for SAEs**

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is



essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

### **6.2.3. Adverse Events of Special Interest**

The investigator or site staff will be responsible for detecting, documenting and reporting events the following AEs of special interest:

- Development of thyroid cancer
- Haematologic malignancy
- Pancreatic cancer
- Pancreatitis
- Injection site reactions
- Immunological reactions (e.g., drug hypersensitivity reactions involving anaphylaxis/anaphylactoid reactions, acute bronchoconstriction, angioedema, and/or acute urticaria)
- Severe hypoglycaemia events (which includes all events meeting the definition of SAEs [Appendix 5](#))
- Hepatic events
- Hepatic enzyme elevations (including GGT)
- Serious GI events
- Appendicitis
- Atrial fibrillation/flutter
- Pneumonia
- Worsening renal function
- Diabetic retinopathy

The results of any investigation should be recorded in the relevant sections of the subjects' eCRFs. In addition, for thyroid, pancreas or haematological malignancies a copy of the histopathology report and a discharge summary if the subject was admitted, or any available case summary (e.g. clinic letter), is to be provided to the Sponsor, if available.

Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. In subjects where a treatment emergent thyroid nodule is identified, if serum calcitonin is measured at the discretion of the Investigator (e.g., per local guidelines) and found to be >100 ng/L this should prompt further investigation for MTC and potential interruption or discontinuation of investigational product until diagnosis has been resolved. If MTC or other thyroid C-cell neoplasia is diagnosed, albiglutide will be discontinued.

A Pancreatitis Adjudication Committee composed of independent specialists in gastroenterology will review all cases of possible pancreatitis.

Subjects should also be closely monitored for signs of potential allergic or drug hypersensitivity reactions including anaphylaxis, angioedema, generalized urticaria, and other potential manifestations of systemic allergic or drug hypersensitivity reactions. A serum sample should be taken as soon as possible after any such event in order to measure antibody to the drug. Instructions for sample processing are in the SRM. These events should be reported as AEs or SAEs based on the clinical evaluation of the subject. The reactions should be followed to completion as typical for any AE or SAE. Subjects with allergic or drug hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology should have investigational product withdrawn and not re-introduced.

Episodes of severe hypoglycaemia will be recorded according to subject report. Severe hypoglycaemic incidents will be defined as those episodes of hypoglycaemic symptoms for which the subject required assistance from another person and from which the subject recovered promptly after oral carbohydrate, intravenous glucose, glucagon administration or other resuscitative actions (definition per ADA Workgroup on Hypoglycaemia [Sequist, 2013]). Additionally, all episodes of hypoglycaemic symptoms which in the investigator's opinion meet the definition of a SAE (defined in [Appendix 5](#)) will be included as severe hypoglycaemic episodes. During this study, if a subject's eGFR approaches 30mL/min/1.73m<sup>2</sup> closer monitoring of renal function is considered prudent, according to standard clinical practice. If eGFR is <15mL/min/1.73m<sup>2</sup> follow the procedure set out in Section [4.4.4](#).

#### **6.2.4. Clinically Important Microvascular Events**

Clinically important microvascular events are defined as the following: need for renal transplant or dialysis, new diabetes-related blindness, and procedures (laser photocoagulation or anti-vascular endothelial growth factor treatment or vitrectomy for diabetic retinopathy/eye disease). Clinically important microvascular events will be reported as recorded in the eCRF by the investigator without adjudication.

The AEs associated with the above outcomes or treatments should be reported separately as an AE or SAE according to the definitions in [Appendix 5](#).

#### **6.2.5. Pregnancy**

- If a subject becomes pregnant during the study they should discontinue Investigational Product.
- Details of all pregnancies in female subjects will be collected after the start of dosing and until the end of the Post-treatment Follow-up Period.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in [Appendix 6](#).

#### **6.2.6. Clinical Laboratory Assessments**

All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule ([Table 1](#)). Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all central laboratory safety parameters will be provided to the site.

If additional non-protocol specified laboratory assessments result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE of special interest or dose modification) the results must be recorded in the CRF.

Refer to the SRM/laboratory manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

The following laboratory assessments will be performed: serum creatinine, HbA1c, liver function tests [AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin, GGT], and urine and serum  $\beta$ hCG pregnancy test (for women of child bearing potential). All study-required laboratory assessments will be performed by a central laboratory, with the exception of HbA1c and creatinine at Screening and urine pregnancy test at Screening/Randomization.

#### **Screening HbA1c and serum creatinine**

Screening HbA1c and serum creatinine values should be based on the most recent local laboratory values taken as part of usual care within the previous 6 months and the values entered into the eCRF. These assessments must have been performed at an accredited laboratory. HbA1c screening results must be either Diabetes Control and Complications Trial (DCCT) aligned or International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardized. HbA1c screening results from point of care equipment are acceptable provided that the equipment is maintained by an accredited laboratory. If HbA1c or creatinine have not been assessed in the previous 6 months, laboratory assessments will be performed via the central laboratory to determine eligibility (if a local laboratory is used in error the results are acceptable for determining eligibility). The

investigator has the discretion to repeat screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.

Re-screening of subjects who did not meet the eligibility criteria for HbA1c or creatinine based on local laboratory values taken as part of usual care is permitted. If values were based on laboratory results as part of usual care then one re-test is permitted within the protocol at Screening. Any future re-screening will be based on laboratory results obtained as part of usual care.

### **Pregnancy testing (for women of childbearing potential)**

At the screening visit perform a urine pregnancy test. If the urine pregnancy test is positive, send a serum blood sample to the central laboratory for confirmation of pregnancy.

At the Randomisation visit perform a urine pregnancy test. If the result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised (provided all other eligibility criteria have been met).

If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. Do not randomise if the urine pregnancy test is positive; send a serum blood sample to the central laboratory for confirmation of pregnancy. If the urine pregnancy test is negative then the subject can be randomised at the same visit (provided all other eligibility criteria have been met).

### **Lipids**

Where serum lipid tests have been performed as part of the subject's routine clinical care (i.e. not as a study procedure) the most recent results should be recorded at baseline and annually thereafter. The lipid parameters to be recorded are total cholesterol (TC), low density lipoprotein cholesterol (LDLc), high density lipoprotein (HDLc) and triglycerides (Tg).

If any or all of these results are not already available from the subject's records then separate lipid tests should not be performed solely for the study.

#### **6.2.6.1. Estimated Glomerular Filtration Rate (eGFR)**

Serum creatinine will be measured every 8 months by a central laboratory. It will be used to calculate eGFR using the MDRD formula [Levey, 2009], namely:

$$\text{eGFR (ml/min/1.73m}^2\text{)} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}).$$

### **6.2.7. Physical examination**

A general physical examination, including height and neck (thyroid), will be performed at randomization. A targeted physical examination will be performed at all other time points as specified in the Time and Events Table ([Table 1](#)). The targeted physical examination will evaluate the cardiovascular system and injection sites and will include measurement of blood pressure and heart rate taken with the subject either in a semi-recumbent or seated position after at least a 5-minute rest period.

## **6.3. Value Evidence and Outcomes**

### **6.3.1. Value Evidence and Outcomes Assessments**

#### **6.3.1.1. Treatment Related Impact Measure – Diabetes (TRIM-D)**

In order to evaluate satisfaction with treatment and to compare satisfaction across treatment groups, the TRIM-D questionnaire will be self administered by all subjects at baseline (except for subjects whose diabetes is treated by diet and exercise alone) and all subjects at each 8 month visit (and, to the extent possible, at the time of study completion or withdrawal from the study).

The TRIM-D, developed in 2009, is a 28-item treatment satisfaction measure scored to produce 5 sub-scale scores (Treatment Burden, Daily Life, Diabetes Management, Psychological Health, and Compliance) as well as a total score. It is available in a wide range of translations.

The TRIM-D development, in accordance with the principles of the Food and Drug Administration Patient Reported Outcome Guidance document, was based on findings from the published literature including content from already-existing treatment satisfaction measures as well as significant input from subjects with type 1 and with type 2 diabetes and from expert diabetes clinicians. The TRIM-D has been evaluated in a sample of 507 subjects (74% with type 2 diabetes) and has been shown to have acceptable reliability and validity [[Brod, 2009a](#)]. Its responsiveness was also evaluated in a sample of 242 subjects (71% with type 2 diabetes) and found to be acceptable [[Brod, 2009b](#)]. Some preliminary work has been done on estimating its minimal important difference but this needs further exploration [[Brod, 2009b](#)].

#### **6.3.1.2. EQ-5D**

The EQ-5D will be self-administered by subjects in order to measure generic health status. Combining the EQ-5D with the disease-specific TRIM-D, which is designed to have maximum sensitivity to relevant aspects of disease related treatment, will provide a more robust evaluation of the impact of treatments for type 2 diabetes and allow for clearer interpretation of study results. TRIM-D results, if consistent with the general trends seen in the EQ-5D, will have enhanced credibility.

The EQ-5D is a standardized instrument used to evaluate generic health-related quality of life. It is applicable to a wide range of health conditions and treatments, and it provides a simple descriptive profile and a single index value for health status. It is also used to provide utilities, or preference weights, for use in economic (cost effectiveness) evaluations. It is available in 141 self complete official language versions.

The EQ-5D has been used extensively in studies to measure the impact of type 2 diabetes and treatments for the disease. A systematic review identified 54 publications reporting EQ-5D responses and 39 papers presenting evidence on the measurement properties of the EQ-5D in this population [Janssen, 2011]. This evidence supported the validity, reliability, and responsiveness of the EQ-5D for evaluating health-related quality of life in subjects with type 2 diabetes. Other studies reported that index scores from the EQ-5D have been shown to be an independent predictor of the risk of mortality, future vascular events, and other complications in people with type 2 diabetes [Clarke, 2009]. In addition, the SHIELD longitudinal study (1,741 respondents with type 2 diabetes and 4,543 without diabetes) used the EQ-5D to assess the 5-year changes in health-related quality of life in type 2 diabetes [Grandy, 2012].

#### **6.3.1.3. Exploratory Diabetes Management Questions**

In addition to the standardised instruments described above, patient experience in relation to the management of their diabetes will be evaluated in a subset of sites using a small number of self-administered diabetes management questions. These types of customized questions have been used successfully in asthma and in diabetes when patients are involved with goal-setting [Juniper, 1992; Anderson, 2010]. This tailored approach is an opportunity to capture data in the study that are not otherwise available from standard PRO measures such as the TRIM-D and the EQ-5D. As an exploratory endpoint, this set of questions (3 items at baseline, and at each 8 month follow-up visit) imposes very little patient or site burden, but can offer critical insight into the one area of the patient's choosing that s/he finds most difficult to manage. In addition, this patient-centred endpoint has the potential to be sensitive to changes over time.

These questions have been developed by GSK based on factors identified as important to subjects in the development of published, validated and reliable subject reported outcomes instruments in type 2 diabetes.

#### **6.3.1.4. Healthcare Resource Utilisation**

Data will be collected on the following healthcare resource use:

- All cause hospitalisations and related healthcare resource use.

Healthcare resource use data will be collected in order to facilitate subsequent health-economic analyses comparing costs between albiglutide added to standard of care and placebo added to standard of care (cost is not an end point in the study).

Data on all-cause hospitalizations and related inpatient healthcare resource use will be collected. This will include:

- All-Cause hospitalisation including: Admission and discharge diagnoses (primary and secondary), length of stay, level/type of ward, and time spent in Intensive Therapy Unit (or equivalent).

#### **6.4. Genetic Research**

Information regarding genetic research is included in [Appendix 1](#).

### **7. DATA MANAGEMENT**

- For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

### **8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS**

#### **8.1. Hypotheses**

This trial will examine the following primary question:

- Whether albiglutide is non inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. Letting  $\lambda_1$  = hazard ratio for time to first MACE for albiglutide vs placebo, then:

Null hypothesis:  $\log \lambda_1 \geq \log(1.3)$

Alternative hypothesis:  $\log \lambda_1 < \log(1.3)$

#### **8.2. Study Design Considerations**

##### **8.2.1. Sample Size Assumptions**

The primary outcome will be analyzed such that the overall Type 1 error is no greater than 5% (two-sided). Specifically, the non-inferiority assessment of albiglutide compared to placebo will be conducted at 0.05 level, requiring one-sided significance at 0.025.

The power for MACE non-inferiority is calculated via the asymptotic variance and normality of the maximum likelihood estimator for the log-hazard ratio. Assuming a true hazard ratio of 1.0, 611 events will be needed to have 90% power to rule out non-inferiority margin of 1.3 for the hazard ratio with type I error of 0.05. The study duration will be event-driven. A total of 9400 subjects will be enrolled and followed until it is projected that approximately 611 adjudicated MACE events will have occurred. If the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years respectively, assuming that the number of subjects lost to follow-up accounts for 1% or less.

### 8.2.2. Sample Size Sensitivity for MACE non-inferiority

9400 subjects will be enrolled to cumulate the first MACE events experienced by 611 unique subjects. The study duration may vary depending on actual MACE event rate and duration of enrolment period.

**Table 3 Total Study Duration Sensitivity for Varying MACE Event Rate and Duration of Recruitment**

MACE rate (% pa)	Duration of recruitment			
	1.5 yrs	2.0 yrs	2.5 yrs	3.0 yrs
2.0	4.1yrs	4.4yrs	4.6yrs	4.9yrs
2.5	3.4 yrs	3.7yrs	3.9yrs	4.2yrs
3.0	3.0yrs	3.2yrs	3.5yrs	3.8yrs
3.5	2.7yrs	2.9yrs	3.2yrs	3.4yrs

### 8.2.3. Sample Size Re-estimation

The aggregate blinded event-rate data will be periodically reviewed by the Executive Committee and the sponsor. The study has an event-driven design. Should emerging data diverge significantly from protocol assumptions, the total sample size and/or follow up time may be adjusted, within the bounds of feasibility, to achieve the event target.

## 8.3. Data Analysis Considerations

### 8.3.1. Analysis Populations

The intent-to-treat (ITT) population will include all randomly assigned subjects. The ITT subjects will be analyzed according to randomised treatment. The inference for primary objectives in the study will be made from ITT population.



Per-protocol Population (PP) will exclude the subjects who have major protocol violations. Per-protocol analysis will include Per-protocol population only and their data upon to the time of discontinuation of investigational product plus 56 days.

The non-insulin population (NI) will include all subjects in the ITT population who are not on insulin at baseline. Inference for the time to insulin endpoint will be made from the NI population.

The baseline basal insulin user population (BI) will include all subjects in the ITT population who are on basal insulin, but not on other insulin at baseline. Inference for the time to prandial insulin endpoint will be made on BI population.

The safety population will include all enrolled subjects who receive at least 1 dose of study treatment. The safety population subjects will be analyzed according to the treatment received. The safety population will be used for analyses of safety objectives.

Other analysis populations will be defined in the RAP.

### **8.3.2. Analysis Data Set**

For time to event data, censoring time for subjects who lost to follow-up is defined as following:

- For primary analysis, subjects who are lost to follow-up will be censored at the date of last evidence of confirmatory status for MACE events.
- For on-treatment analysis, censoring date will be the last dose date.
- For on-therapy analysis (on-treatment+56 days), censoring date will be the last dose date+56 days.
- For analysis of all cause of mortality, censoring date will be the latest date known alive.

### **8.3.3. Treatment Comparisons**

Demographic and baseline characteristics (e.g., gender, age, racial or ethnic origin, height and weight, body mass index (BMI), blood pressure and other characteristics) will be summarized for each treatment group. In addition, smoking and alcohol habits, diabetic and cardiovascular medical history, baseline laboratory results, and prior medications will be summarized by treatment group. Binary and ordinal characteristics will be summarized by counts and percentages, while continuous variables will be represented by mean and standard deviations or medians and percentiles, as appropriate. Any variables with treatment imbalances may be considered as covariates for further analysis of an exploratory nature. Such covariates will be identified on the basis of the clinical relevance of the observed treatment difference.

### **8.3.3.1. Primary Comparisons of Interest**

The primary endpoint will be the time to the first occurrence of MACE over the full duration of the study. A p-value for the primary endpoint will be calculated from a Cox Proportional Hazards (PH) regression model with treatment group as the only covariate for the hypotheses described in Section 8.1.

### **8.3.3.2. Other Comparisons of Interest**

For other analyses incidence rates will be presented for binary data and summary statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous data. Time to event endpoints will be evaluated via the p-value from a Cox PH regression model with treatment as the only covariate. Furthermore, summary statistics of change from baseline for HbA1c will be presented along with percent of subjects within ranges of clinical interest (e.g., HbA1c < 7.0%). Available lipid data will be summarized for descriptive purposes.

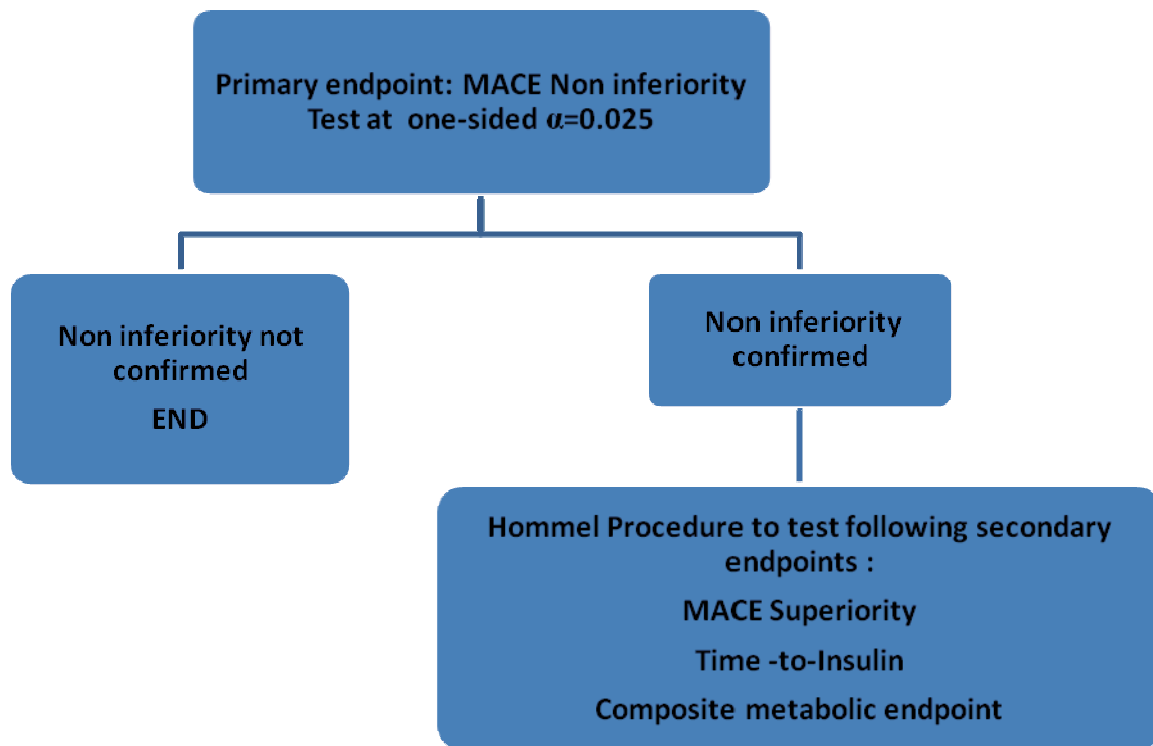
### **8.3.4. Interim Analysis**

An IDMC will monitor progress of the study and ensure that it meets the highest standards of ethics and subject safety. All cardiovascular event data, together with other safety data, will be sent to the IDMC for review at approximately every 6 months after the first subject has been randomised to receive treatment. This frequency may be adjusted, if deemed necessary by the IDMC, depending on the enrolment rates and the rate of safety events. There are no plans to stop the study early for a non-inferiority or benefit claim, however should the IDMC identify in the course of its scheduled reviews overwhelming evidence of MACE benefit (e.g.,  $p < 0.001$ ), with directionally consistent findings on all-cause mortality, the IDMC might consider recommending early stopping. This approach essentially preserves the final alpha for the end-of-study analysis at 5% and hence there are no plans to adjust the final alpha on account on safety reviews conducted by the IDMC. The IDMC charter, reporting and procedures are outlined in separate documents.

### **8.3.5. Multiplicity Controls**

A multiple comparisons adjustment strategy will be implemented for the multiple inferential tests among the primary endpoint and secondary endpoints of MACE superiority, time to insulin and composite metabolic endpoint.

The strategy will use a combination of gatekeeper and Hommel procedure. The first step is to evaluate the MACE non-inferiority of the albiglutide group vs the placebo group at a one-sided  $\alpha=0.025$  level. If the result of non-inferiority is significant, MACE superiority, time-to-insulin and composite metabolic endpoint will be tested simultaneously using the Hommel procedure with  $\alpha=0.05$ . The above multiplicity control approach will preserve the study's nominal significance level of 0.05. The test order is illustrated in the diagram below.



Hommel Procedure for secondary endpoints is described below:

Three hypothesis tests for MACE superiority, time-to-insulin, and composite metabolic endpoint are subject to be adjusted by the Hommel procedure. Let  $P(1)$ ,  $P(2)$  and  $P(3)$  represent the ordered p-values that  $P(3) > P(2) > P(1)$  and  $H(1)$ ,  $H(2)$  and  $H(3)$  are corresponding hypotheses.

If  $P(3) < 0.05$ , reject  $H(3)$ ,  $H(2)$ ,  $H(1)$ . End of test.

If  $P(3) \geq 0.05$  and  $P(2) < 0.05/2$ , accept  $H(3)$ , reject  $H(2)$ ,  $H(1)$ . End of test.

If  $P(3) \geq 0.05$  and  $P(2) \geq 0.05/2$  and  $P(1) < 0.05/3$ , accept  $H(3)$ ,  $H(2)$ , reject  $H(1)$ . End of test.

If  $P(3) \geq 0.05$ ,  $P(1) \geq 0.05/3$  and  $0.05/2 \leq P(2) < 0.05 \cdot 2/3$ , accept  $H(3)$ ,  $H(2)$ , reject  $H(1)$ . End of test.

If  $P(3) \geq 0.05$ ,  $P(2) \geq 0.05 \cdot 2/3$  and  $P(1) \geq 0.05/3$ , accept  $H(3)$ ,  $H(2)$  and  $H(1)$ .

#### *Other Secondary Endpoints and Subgroup Analysis*

The following secondary endpoints will provide supportive evidence for cardiovascular safety and will not use any multiplicity adjustment procedure.

- Components of primary endpoint (MACE = cardiovascular death, MI, stroke)
- MACE + urgent revascularisation for unstable angina
- Cardiovascular death or hospitalisation for heart failure

Other secondary endpoints which do not qualify for formal statistical hypothesis testing will be analyzed and have results presented with confidence interval and nominal p-values:

- Mean HbA1c at scheduled visits and change from baseline
- Mean body weight at scheduled visits and change from baseline
- Mean eGFR at scheduled visits and change from baseline
- Time to initiation of prandial insulin
- Composite microvascular endpoint

To examine the degree of consistency of the overall treatment effect in terms of important prognostic factors, subgroup analyses of the primary outcomes will be performed based on subject demographics and baseline characteristics. These exploratory subgroup analyses will not be adjusted for multiple comparisons and will be interpreted descriptively.

### **8.3.6. Key Elements of Analysis Plan**

Any deviations from the original analysis planned in the protocol agreed upon prior to finalization of the RAP, will be described in that document. Any additional changes to the planned analysis in the RAP will be described in the final clinical study report.

#### **8.3.6.1. Primary Analysis**

The primary analysis is an ITT analysis of the time to the first occurrence of MACE over the full duration of the study. Time to event analyses will be performed using Cox's Proportional Hazard regression with SAS PHREG with treatment group as the only covariate. Data for subjects without a primary event will be censored.

Treatment differences will be estimated via the hazard ratio and its 95% confidence interval (CI).

The hypothesis of non-inferiority of albiglutide relative to placebo group with hazard ratio less than 1.3 with respect to cardiovascular risk will be tested at the end of the study when ~611 first MACE events are cumulated.

The strength of evidence for non-inferiority will be determined by testing the hypothesis that the observed hazard ratio is significantly different from the null margin of 1.3 (one-sided  $p < 0.025$  for such a test being equivalent to the upper 95% confidence limit after multiplicity adjustment for the hazard ratio being less than 1.3). The absolute risk difference per 100 PY and superiority p-value for albiglutide vs. placebo will also be presented.

The product-limit estimates of the probabilities (and their standard errors) of first MACE over time will be computed and displayed as Kaplan-Meier (KM) survival curves for albiglutide and placebo groups. The KM curves will also be presented corresponding to the above comparisons.

The total number of all MACE or any of its components will be analyzed by Poisson regression model. The incidence rate per 100 person-years, relative risk and their 95% CI will be presented. Number of subjects who experienced at least one event, 2 or 3 or more MACE or its components will also be summarized by treatment group.

As sensitivity analyses, the analyses described above will be repeated using events occur while on-treatment and events occur during the period of on-treatment plus 56 days post last dose.

### **8.3.6.2. Secondary Endpoint Analysis**

Endpoints that supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes endpoints:

- MACE superiority will be evaluated using the same Cox regression model as the primary analysis of MACE non-inferiority.
- Supportive endpoints including the time to first occurrence of adjudicated MACE or urgent revascularisation for unstable angina, time to first occurrence of individual components of MACE, time to first occurrence of cardiovascular death or hospitalisation for heart failure will be analyzed using a proportional Cox regression model similarly as the primary endpoint.

Endpoints that evaluate the effects of albiglutide on metabolic management of type 2 diabetes:

- Among the subjects who are not on insulin at baseline (NI population), time to insulin will be analyzed using a proportional Cox regression model similar to the primary MACE analysis. The product-limit estimates of the probabilities (and their standard errors) of adding insulin over time will be computed and displayed as Kaplan-Meier (KM) survival curves for albiglutide and placebo treatment groups. The KM curves will also be presented corresponding to the above comparisons.
- Composite of the proportion of those achieving good control ( $HbA1c \leq 7.0\%$ ) AND no severe hypoglycaemic incidents AND weight gain  $<5\%$  at the end of the study would be evaluated utilize nonparametric, covariance-adjusted, extended Mantel-Haenszel tests. Additional analysis will be provided for scheduled visits. Nominal p-values and 95% CIs will be presented for these visits. Time to introduction of prandial insulin in those on basal insulin  $\pm$  orals anti-hyperglycemic drugs at baseline will be analyzed using a Cox PH model and KM method similar to the primary endpoint.
- Composite of microvascular events will be analyzed using a proportional Cox regression model and KM method similar to the primary endpoint.

- HbA1c, body weight and eGFR will be analyzed using a repeated mixed effect model. The least square means, 95% CIs and nominal p-values will be presented.
- Additional analysis will be performed to assess the incidence rate of recurrent severe hypoglycaemic events between treatment groups during the course of the study. A repeated Poisson regression model including treatment and visit as factors will be used to test treatment difference with offset for person years. An unstructured working correlation matrix will be used in the iterative estimation process. The model-adjusted least square incidence rate for each treatment as well as the treatment difference of the incidence rate will be reported. Events of severe hypoglycaemia will also be summarized descriptively by treatment group. Additional summary by baseline HbA1c, renal status and age subgroup will also be provided.

Further analysis details will be provided in the RAP.

#### **8.3.6.3. Subgroup Analysis**

Separate subgroup analyses of the primary outcomes will be performed based on subject demographics and baseline characteristics. Subgroups may include sex, age group, BMI, whether subjects have history of a previous cardiovascular event, and baseline HbA1C, background of anti-hyperglycaemia treatment etc. The detail of subgroups will be pre-specified in the RAP. Consistency of treatment effects will be assessed using Cox regression, along with the 95% confidence intervals for the relative risk or hazard ratios for each subgroup a nominal alpha level for interaction of 0.10 will be used. The effect of treatment interaction with subgroups will also be explored; however as the number of these subgroup variables may be large, the probability of observing at least one statistically significant result may be high. Thus these additional analyses will be considered exploratory regardless of the p-value associated with any interaction.

Further details will be provided in the RAP.

#### **8.3.6.4. Other Safety Analyses**

Subject demographics, medical history, prior and concomitant medications, vital sign measurements, laboratory values, physical examination assessments, will be summarized by treatment group using descriptive statistics.

For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages.

For SAEs, AEs leading to permanent IP withdrawal and AEs of special interest, the number and percentage of subjects, total number of events and incidence density will be presented by treatment group and overall at the SOC and Preferred Term (PT) level. Relative Risk and its 95% CI may also be presented on a targeted basis. The time to first occurrence of specific events will be summarized.

All cause mortality will be summarized by treatment group and analyzed using a Cox PH model similarly as the-primary endpoint.

All events sent to CEC (including TIAs) will be summarized.

Pancreatitis events will be adjudicated by the independent Pancreatitis Adjudication Committee. The information for investigator reported pancreatitis events and its adjudication results will be summarized.

Further analysis details will be provided in the RAP.

#### **8.3.6.5. Value Evidence and Outcomes Analyses**

TRIM-D total score and score for each domain will be summarized descriptively by treatment group and scheduled visit. Score changes from baseline will be compared between treatments for each visit by an ANCOVA model.

For EQ-5D, subjects' responses at each visit for the 5 domains will be summarized categorically by treatment group, together with the summary of utility score at each visit and change from baseline by treatment group. Change from baseline will be compared between treatment groups for each visit by an ANCOVA model.

For study specific PRO questions, responses will be summarized descriptively by treatment group and scheduled visit.

Healthcare resource use will be summarized by treatment group and visit.

Further analysis details will be provided in the RAP.

## **9. STUDY CONDUCT CONSIDERATIONS**

### **9.1. Posting of Information on Publicly Available Clinical Trial Registers**

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

### **9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process**

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

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH E6 Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favourable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

Signed informed consent must be obtained for each subject prior to participation in the study

The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research. Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission. Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

### **9.3. Quality Control (Study Monitoring)**

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

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

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

### **9.4. Quality Assurance**

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the



regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

## **9.5. Study and Site Closure**

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

## **9.6. Records Retention**

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

### **9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication**

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

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

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.

### **9.8. Independent Data Monitoring Committee (IDMC)**

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter.

### **9.9. Pancreatitis Adjudication Committee**

Detailed information on suspected pancreatitis events will be collected on special pages of the eCRF. A Pancreatitis Adjudication Committee composed of independent specialists in gastroenterology will review cases of possible pancreatitis. Details of this

committee and case adjudication are described in the committee's charter available on request.

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## 11. APPENDICES

### 11.1. Appendix 1: Genetic Research

#### Background

Genetics is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of genetic associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	<i>HLA-B*57:01</i> (Human Leukocyte Antigen B)	Carriage of the <i>HLA-B*57:01</i> variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective <i>HLA-B*57:01</i> screening and exclusion of <i>HLA-B*57:01</i> positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labelling in the United States and Europe now recommend (US) or require (EU) prospective <i>HLA-B*57:01</i> screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. <i>HLA-B*57:01</i> screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	<i>HLA-B*15:02</i>	Independent studies indicated that patients of East Asian ancestry who carry <i>HLA-B*15:02</i> are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of <i>HLA-B*15:02</i> prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	<i>UGT1A1*28</i>	Variations in the <i>UGT1A1</i> gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular <i>UGT1A1</i> gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the <i>UGT1A1*28</i> variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful genetic research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable genetic analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to albiglutide.

### Genetic Research Objectives

The objective of genetic research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to albiglutide. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with albiglutide, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Safety and/or tolerability
- Efficacy

### Study Population

Any subject who is enrolled in the clinical study, can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from genetic research.

Subject participation in the genetic research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.



## Study Assessments and Procedures

Blood samples can be taken for deoxyribonucleic acid (DNA) extraction and used in genetic assessments.

If taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (~6ml) will be collected for the genetic research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomised and provided informed consent for genetic research, but may be taken at any time while the subject is participating in the clinical study.

- The genetic sample is labelled (or “coded”) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilise the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct genetic analysis may be identified after a study (or a set of studies) of albiglutide has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to albiglutide.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

## Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in genetic research with the genetic sample retained for analysis
- Withdraw from genetic research and destroy the genetic sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in

the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time when a subject wishes to withdraw from genetic research or have their sample destroyed whether during the study or during the retention period following close of the main study.

### **Screen and Baseline Failures**

If a blood sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

### **Analyses**

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to albiglutide. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and genetic research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of genetic investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

### **Informed Consent**

Subjects who do not wish to participate in genetic research may still participate in the clinical study. Genetic informed consent must be obtained prior to any blood being taken for genetic research.

## Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarise the genetic research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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## 11.2. Appendix 2: GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

1. Contraceptive subdermal implant that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label.
2. Intrauterine device or intrauterine system that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Trussell, 2011]
3. Oral Contraceptive, either combined or progestogen alone [Trussell, 2011]
4. Injectable progestogen [Trussell, 2011]
5. Contraceptive vaginal ring [Trussell, 2011]
6. Percutaneous contraceptive patches [Trussell, 2011]
7. Male partner sterilization prior to the **female subject's entry** into the study, and this male is the sole partner for that subject. The information on the male sterility can come from interview with the subject on her male partner's medical history.
8. Male condom **combined with a female** diaphragm, with or without a vaginal spermicide (foam, gel, film, cream, or suppository). In the UK it is a country-specific requirement of the regulatory authority (Medicines and Healthcare Products Regulatory Agency) that a vaginal spermicide be used.

These allowed methods of contraception have a failure rate of less than 1% per year but are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

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### 11.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

**Phase III-IV liver chemistry stopping and increased monitoring criteria** have been designed to assure subject safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).

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

#### Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
<b>ALT-absolute</b>	ALT $\geq$ 8xULN
<b>ALT Increase</b>	ALT $\geq$ 5xULN but <8xULN persists for $\geq$ 2 weeks ALT $\geq$ 3xULN but <5xULN persists for $\geq$ 4 weeks
<b>Bilirubin<sup>1,2</sup></b>	ALT $\geq$ 3xULN <b>and</b> bilirubin $\geq$ 2xULN (>35% direct bilirubin)
<b>INR<sup>2</sup></b>	ALT $\geq$ 3xULN <b>and</b> INR>1.5, if INR measured
<b>Cannot Monitor</b>	ALT $\geq$ 5xULN but <8xULN and cannot be monitored weekly for $\geq$ 2 weeks ALT $\geq$ 3xULN but <5xULN and cannot be monitored weekly for $\geq$ 4 weeks
<b>Symptomatic<sup>3</sup></b>	ALT $\geq$ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> <li>Immediately discontinue study treatment</li> <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 subject until liver chemistries resolve, stabilize, or return to within baseline (see <b>MONITORING</b> below)</li> <li><b>Do not restart</b> subject with study treatment unless allowed per protocol and GSK Medical Governance approval <b>is granted</b> (refer to</li> </ul>	<ul style="list-style-type: none"> <li>Viral hepatitis serology<sup>4</sup></li> <li>Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody<sup>5</sup>.</li> <li>Blood sample for pharmacokinetic (PK) analysis, obtained within 3 half lives (15 days) of last dose<sup>6</sup></li> <li>Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</li> <li>Fractionate bilirubin, if total bilirubin <math>\geq</math> 2xULN.</li> </ul>

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<p><a href="#">Appendix 5</a>)</p> <ul style="list-style-type: none"> <li>• <b>If restart is not granted</b>, permanently discontinue study treatment and continue subject in the study for any protocol specified follow up assessments</li> <li>• Re-challenge is not allowed.</li> </ul> <p><b>MONITORING:</b></p> <p><b><u>For bilirubin or INR criteria:</u></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 hrs</b></li> <li>• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline</li> <li>• A specialist or hepatology consultation is recommended</li> </ul> <p><b><u>For All other criteria:</u></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> </ul> <p>Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline</p>	<ul style="list-style-type: none"> <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, other over the counter medications.</li> <li>• Record alcohol use on the liver event alcohol intake case report form</li> </ul> <p><b><u>For bilirubin or INR criteria:</u></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 pressure liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [<a href="#">James</a>, 2009]). <b>NOTE: not required in China</b></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 subject if ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN (>35% direct bilirubin) or ALT  $\geq$  3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

### Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
<p>ALT <math>\geq</math>5xULN and &lt;8xULN <b>and</b> bilirubin &lt;2xULN <b>without</b> symptoms believed to be related to liver injury or hypersensitivity, <b>and</b> who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT <math>\geq</math>3xULN and &lt;5xULN <b>and</b> bilirubin &lt;2xULN <b>without</b> symptoms believed to be related to liver injury or hypersensitivity, <b>and</b> who can be monitored weekly for 4 weeks.</p>	<ul style="list-style-type: none"> <li>• Notify the GSK medical monitor <b>within 24 hours</b> of learning of the abnormality to discuss subject safety.</li> <li>• Subject can continue study treatment</li> <li>• Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline</li> <li>• If at any time subject meets the liver chemistry stopping criteria, proceed as described above</li> <li>• If ALT decreases from ALT <math>\geq</math>5xULN and &lt;8xULN to <math>\geq</math>3xULN but &lt;5xULN, continue to monitor liver chemistries weekly.</li> <li>• If, after 4 weeks of monitoring, ALT &lt;3xULN and bilirubin &lt;2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.</li> </ul>



**References**

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

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol.* 2005;43(5):2363–2369.

#### 11.4. Appendix 4: Liver Safety Drug Restart Guidelines

If subject meets liver chemistry stopping criteria do not restart subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the subject

If GSK Medical Governance approval to restart the subject with study treatment **is not granted**, then the subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

##### ***Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment***

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury) or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section [6.2.2](#) and [Appendix 5](#)

## **11.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events**

### **11.5.1. Definition of Adverse Events**

<b>Adverse Event Definition:</b>
<ul style="list-style-type: none"><li>• An AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</li><li>• NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.</li></ul>



<b>Events <u>meeting</u> AE definition include:</b>
<ul style="list-style-type: none"><li>• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.</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 prior to the start of the study.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).</li><li>• The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.</li></ul>

**Events NOT meeting definition of an AE include:**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

**11.5.2. Definition of Serious Adverse Events**

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, etc).

**Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:**

**a. Results in death****b. Is life-threatening**

NOTE:

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

**c. Requires hospitalization or prolongation of existing hospitalization**

NOTE:

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

**d. Results in disability/incapacity**

## NOTE:

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

**e. Is a congenital anomaly/birth defect****f. Other situations:**

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

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

- $ALT \geq 3 \times ULN$  and total bilirubin\*  $\geq 2 \times ULN$  (>35% direct), **or**
- $ALT \geq 3 \times ULN$  and  $INR^{**} > 1.5$ .

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

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

### 11.5.3. Recording of AEs and SAEs

#### **AEs and SAE Recording:**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

#### 11.5.4. Evaluating AEs and SAEs

##### Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

##### Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.



**Follow-up of AEs and SAEs**

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

**11.5.5. Reporting of SAEs to GSK****SAE reporting to GSK via electronic data collection tool**

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the safety designee as detailed in the Study Reference Manual
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- Site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

## **11.6. Appendix 6: Collection of Pregnancy Information**

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, 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 5](#). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

### **Any female subject who becomes pregnant while participating**

- will discontinue study medication

## **11.7. Appendix 7: Electronic Health Record Ancillary Study**

### **11.7.1. Introduction**

#### **11.7.1.1. Background**

Clinical researchers and policy makers want to move towards embedding clinical trials directly within health care delivery systems in order to increase the relevance, speed, and efficiency of clinical research [Richesson, 2013]. The assumption is that the capabilities offered by Electronic Health Records (EHRs), along with concurrent changes in health care organization and delivery, and the development of a learning health system will transform the way clinical research is conducted [Etheredge, 2007; Greene, 2012].

In 2011, the National Heart, Lung, and Blood Institute (NHLBI) convened the NHLBI Working Group on Electronic Health Records: Research Priorities to Improve Cardiopulmonary Health in Clinical Practice. As part of their mission, this working group identified key research, policy, and training priorities [Curtis, 2014]. A key research priority was to leverage EHR tools to facilitate the efficient implementation of randomized clinical trials. Specific areas highlighted for increased efficiency included efficient data collection and outcome surveillance and confirmation.

#### **11.7.1.2. Literature Review**

Electronic Health Records were primarily designed to document patient care and facilitate billing and reimbursement. The large amount of electronic data that are captured may also facilitate clinical research and public health surveillance.<sup>5</sup> Despite the complexity of EHR data, national networks have begun to use these data to improve public health and generate real-world evidence [Toh, 2012]. The Patient Centered Outcomes Research network (PCORnet) (pcornet.org) is a research network that is currently being designed to support observational comparative effectiveness research and clinical trials that are embedded in clinical care settings [Fleurence, 2014]. Similarly, the NIH Health Care Systems Research Collaboratory (nihcollaboratory.org) is creating infrastructure to improve the conduct of embedded clinical trials. One ongoing NIH Collaboratory trial is the Time to Reduce Mortality in End-Stage Renal Disease study (TiME) (clinicaltrials.gov identifier: NCT02019225). TiME is a large cluster-randomized, pragmatic trial that will evaluate the effects of systematic implementation of hemodialysis sessions of at least four hours versus usual hemodialysis care. The trial involves data acquisition from EHR systems through a partnership between academic investigators and two health care provider organizations with different electronic data systems. There are several other recent examples of clinical trials that were embedded in health care delivery systems [Gulliford, 2014; van Staa, 2014]. For instance, one recent study evaluated the use of an electronic decision support tool to improve risk factor control (i.e., blood pressure and cholesterol) following a cerebrovascular event with outcome data collected from the EHR [Dregan, 2014]. While the specific intervention was not shown to be efficacious, data acquisition via EHR sources was robust and implemented at a low cost.

### 11.7.1.3. Ancillary Study Rationale

Despite these earlier studies demonstrating the potential opportunities with EHR-based data acquisition, our understanding of how EHR-based platforms might increase the efficiency of data collection, outcome surveillance, and confirmation in an integrated manner is unknown. EHRs are inherently heterogeneous, with each implementation different from the next. The barriers to using EHR-generated lists of patients to facilitate trial enrolment, the fitness of EHR data for populating baseline characteristics in an electronic case report form (eCRF) and the use of EHR data to find events of interest during trial follow-up are not well characterized.

EHR systems contain a wealth of clinical data about patients who are connected to the health care delivery system and may be eligible for enrollment in a clinical trial. Anecdotal reports suggest that identification of potential patients using the EHR increases the number of patients to be screened but may not consistently translate to an increased number of patients enrolled. Causes are likely multi-factorial and may include the translatability of inclusion and exclusion criteria to structured clinical data, the algorithm used to identify potential patients, institutional restrictions regarding unsolicited patient contact, and others. There is a need to empirically assess the barriers to using an EHR-generated list of patients to facilitate trial enrollment.

Structured data captured in the EHR may be similar to data elements specified in baseline patient characteristics in the eCRF, yet EHR data are collected primarily to support clinical care and reimbursement needs. Their fitness for use as source data for selected data elements of the baseline patient characteristics in the eCRF has not been established.

During routine trial follow-up, study coordinators typically gather information from various sources including direct patient contact and medical records of the enrolling institution and outside facilities to document events for study participants. Evidence from the West of Scotland Coronary Prevention Study suggests that cardiovascular endpoints can be ascertained from routinely recorded EHR-type data, but classification was imperfect [Barry, 2013]. There is a need to specifically assess the utility of EHR data acquisition for follow-up events across multiple health systems.

In summary, the EHR is a rich source of clinical data, but is designed specifically to support clinical care delivery and reimbursement needs. The assumption that EHR data are fit for use in high-quality clinical research has not been rigorously evaluated. To provide evidence to address this knowledge gap, GlaxoSmithKline (GSK) and Duke Clinical Research Institute (DCRI) are committed to conducting an exploratory EHR Ancillary Study embedded within a large pragmatic clinical trial at selected study sites. The overarching goal is to further our understanding of how EHR data can be organized into a query-able format to facilitate a more efficient, reliable, and cost-effective research process. The proposed empirical work is exploratory in nature and both qualitative and quantitative.

## **11.7.2. Ancillary Study OBJECTIVES**

### **11.7.2.1. Primary Objectives**

#### **Objective 1: Assess the barriers to using an EHR-generated list of patients to facilitate trial enrollment.**

Through site study coordinator surveys, workflow assessment, analysis of electronic screening logs, comparisons of enrolled patients with patients identified via algorithm, this retrospective objective will describe the screening “funnel” and identify factors responsible for narrowing the funnel from the pool of potentially eligible patients to those enrolled in the clinical trial. Barriers for using EHR systems for this purpose will be assessed at the site level and common cross-site themes will be identified.

#### **Objective 2: Evaluate the fitness of EHR data for use in populating the baseline characteristics in the eCRF**

After study completion and within selected data areas (e.g., demographics, medical history, concomitant medications), the level of agreement between data extracted from the EHR and data documented on the baseline eCRF (reference standard) will be evaluated. Additionally the performance of algorithms developed to identify comorbidities and other clinical concepts will be assessed at the site level and aggregated, where appropriate.

#### **Objective 3: Explore the use of EHR data to find events of interest during trial follow-up**

Case-finding algorithms will be developed for select specified endpoints (i.e., myocardial infarction, stroke, unstable angina, heart failure as outlined in the main study protocol), run during the conduct of the trial, and used to identify potential cases for follow-up by the study coordinator. The site study coordinator will record the dispensation of each potential case so that reconciliation can occur between eCRF documented events and EHR-generated potential events. Safety event reporting will proceed as outlined in the main study protocol (Main Protocol Section 6.2). At the conclusion of the study, the yield of case-finding algorithms will be evaluated along with the performance of EHR-based algorithms with eCRF-reported as well as adjudicated eCRF-reported events (reference standard).

### **11.7.2.2. Secondary Objective**

As a secondary objective, an assessment of the general utility and feasibility of EHR-based outcome acquisition from the coordinator perspective through surveys and standardized workflow assessments will be conducted.

### **11.7.3. Ancillary Study design**

#### **11.7.3.1. Study Design**

The ancillary study will occur in the context of the HARMONY-Outcomes trial, a randomised, double blind, parallel-group, placebo-masked, controlled study to evaluate the effect of albiglutide on cardiovascular events in patients with Type 2 diabetes. Albiglutide will be administered subcutaneously once weekly in a population of patients with Type 2 diabetes and a previous history of cardiovascular disease and who do not have optimal glycaemic control). The duration of the ancillary study will mirror that of the HARMONY-Outcomes trial. The number of sites that will participate in the ancillary study depends upon the outcome of the site EHR capabilities assessment described in Section [11.7.3.2](#) (Site Selection) below. Five study sites recruiting 12-15 subjects each would enable a descriptive assessment of Objectives 1 and 2, whilst, if feasible, 500-1000 subjects at EHR-enabled sites would permit greater precision to be achieved in the assessment of Objective 3.

#### **11.7.3.2. Site Selection**

Sites from the main trial will be selected to participate. As part of the overall site selection process for the main trial, potential sites complete a feasibility survey to gauge their suitability for participation in the HARMONY-Outcomes trial. In addition to questions regarding experience with long-term outcome trials in general and specific features of the planned trial, the feasibility survey includes questions about site readiness for an EHR-facilitated trial. Specific topics include:

- Existence of an EHR system;
- Current use of EHR to screen for potential study participants;
- Types of information currently contained in EHR (inpatient visits, outpatient visits, laboratory results, medications)
- Prior participation in a study that used EHR data for patient screening, follow-up, and/or data collection; and
- Local EHR support to assist with research studies.

Sites who meet minimum qualifications based on this survey (respond affirmatively regarding the existence of an EHR system and local EHR support to assist with research studies), and who have confirmed an interest in participating in the ancillary study will be approached for a more in-depth assessment of capabilities. Specific topics include:

- Current capability to extract EHR-type data from a data warehouse;
- Data domains currently included in the data warehouse (e.g., demographics, vital signs, diagnoses, procedures, medications prescribed, laboratory tests, and death);

- Coding terminologies used for each domain of data;
- Institutional processes and policies for using EHR-type data for clinical research;
- Institutional experience extracting, transforming, and loading warehouse data into a research DataMart that conforms with standardized specifications; and
- Familiarity with or participation in distributed research networks.

Subsequent structured discussions with individual sites may be necessary to explore capabilities and suitability for the ancillary study. For example, engagement of the health system's Information Technology (IT) personnel will be essential but is challenging to gauge in a written survey. Key site selection criteria include:

- Fully implemented EHR system
- Access to an enterprise data warehouse or clinical data repository that stores structured data from the EHR and is updated at least weekly.
- Availability of necessary data
- Engagement of health system IT and analytical personnel

The advantage of a multi-stage, rapid assessment of capabilities is that it allows for a relatively short feasibility survey that can be completed reliably by a study coordinator. Detailed technical questions are reserved for the individuals who provide EHR support for research studies.

#### **11.7.3.3. Data Flows**

The methods for data extraction and capture will require a partnership between study site teams (site principal investigator, site study coordinator, and site technical support), GSK, and the DCRI Data Management Team.

The study will utilize PopMedNet, a software application that enables the creation, operation, and governance of research networks. It allows partners to maintain physical and operational control over their data while allowing authorized users to send queries to the data. PopMedNet consists of two layers: a security layer where access controls and permissions are established and a layer of virtual pipes through which questions are sent from requestor to responder. The PopMedNet software consists of a web-based "network portal" and a DataMart Client application that is installed at each site. PopMedNet employs a "publish-and-subscribe" architecture that does not require a hole through an institutional firewall, but rather allows institutions to pull a query behind the firewall for manual or automated execution.

In research networks with a common data model, PopMedNet is used to distribute executable code that institutions can choose to pull behind their firewall, run against the data in that appropriate format, and return results to the requestor. Security documentation will be provided to all participating sites.

The data flow for this ancillary study will be as follows:

- a) The study site's EHR system will not be changed and will continue to operate as implemented. Data from the thousands of tables in the EHR will be integrated on a nightly basis into a data warehouse that supports research needs (the term EHR is used to mean the system that collects, displays, and stores transactional health care data).
- b) With guidance from the DCRI Data Management Team, the study site's technical team will extract, transform, and load data from the enterprise data warehouse (or clinical data repository) to a Cohort DataMart according to the specifications of the common data model. A common data model standardizes the definition, content and format of data across sites to enable efficient, cross-site querying. The Cohort DataMart will be refreshed from the existing Data Warehouse on a biweekly basis. The Cohort DataMart includes Protected Health Information (PHI) for a broadly defined cohort of potential study participants and will remain behind institutional firewalls.
- c) Data from Pre-Screening logs completed as part of the main study will be captured in a database stored in the same area as the Cohort DataMart to facilitate characterization of the screening funnel. Data from the pre-screening log will enable comparisons of characteristics of potential participants identified via algorithm with patients screened and enrolled.
- d) When a participant is randomized into the study, the study coordinator will enter key subject identifiers (the main trial identifier (ID), Medical Record Number (MRN) equivalent, study randomization date) into the Key Identifier spread sheet.
- e) Via PopMedNet, the DCRI Data Management Team will distribute code that extracts data for randomized participants from the Cohort DataMart into the Study DataMart using the Key Identifier table. Trial ID and randomization date from the Key Identifier table will be included in the Study DataMart. Data for randomized patients at each site will be returned to the DCRI via the HARMONY-Outcomes trial EHR Ancillary Study Query Portal.
- f) Via PopMedNet, the DCRI will distribute executable code (e.g., SQL program) that will query the Study DataMart for potential study endpoints. [See Section [11.7.3.4.1b](#) for case-finding algorithm].
- g) Potential cases (identified via case-finding algorithm) will be returned to the Study Coordinator who will record the dispensation of each potential case in the Case-finding Dispensation Log stored in the Study DataMart (i.e., recorded in the eCRF/not recorded in the eCRF and reasons).
- h) The Study DataMart containing randomized patient data will be transferred from each site to the DCRI on a regular basis (anticipated quarterly with specific frequency to be determined).
- i) Required data elements from the main clinical trial dataset for EHR Ancillary Study sites will be transferred from GSK to the DCRI after the completion of the study. The DCRI will merge data elements from the main clinical trial dataset with Study DataMart data to create the EHR Ancillary Study Dataset.



#### **11.7.3.4. Study Procedures and Processes**

##### **11.7.3.4.1. DCRI**

###### **a) Establish broad definition of cohort**

A broad cohort identification algorithm will be developed based on selected inclusion criteria outlined in the main study protocol. Selected criteria for inclusion into the cohort include:

- Age > 40 years old
- Diagnosis of Type 2 diabetes, broadly defined by diagnosis codes and medications prescribed (See 4.4 for information about algorithms to be used.)
- Established cardiovascular disease (See Section 11.7.4.4 for information about algorithms to be used)

Participating sites will be required to run the “cohort algorithm” within their EHR systems to create the Cohort DataMart which will be used as a basis for Objective #1.

###### **b) Specify contents of the EHR Ancillary Study research DataMart**

EHR data are stored in many different ways. A common data model standardizes the definition, content and format of data across sites to enable a single standardized view that can be used for querying. Sites participating in this ancillary study will be required to transform their data into a common data model that will be designed to be intuitive and user-friendly. Investigators and analysts with prior experience using research data will not need additional skills or knowledge to use the common data model. The DCRI team will manage questions and issues that arise regarding transforming data into the CDM.

The EHR Ancillary Study Common Data format will be adapted from the Patient Centered Outcomes Research Network (PCORnet) Common Data Model (<http://pcornet.org/resource-center/pcornet-common-data-model/>) and may include the following data areas:

- Demographic
- Encounter
- Diagnosis
- Procedure
- Medications prescribed
- Laboratory results, selected

**c) Develop data characterization routines**

As previously described, participating sites will transform local data into the study common data model. The DCRI Data Management Team will develop and distribute code to query the content of tables formatted according to the common data model. The distributed code will generate aggregate output tables that help determine whether the data conform to specifications, maintain integrity across variables and across tables, and trend as expected over time. The data quality review and characterization process will help to ensure that the data meets reasonable standards for data transformation consistency and quality.

DCRI's team will evaluate the creation of the Cohort DataMart using standard programs distributed to each study site for execution behind institutional firewalls.

**d) Develop and distribute test queries**

A series of simple test queries will be developed and distributed to sites for execution against a simulated data set, structured according to the common data model. The test queries will help each site become familiar with PopMedNet and distributed querying without concern about querying against protected health information.

**e) Develop algorithms for analytic variables**

Algorithms to map EHR-based data in the Study DataMart to baseline characteristics and study endpoints in the EHR Ancillary Study dataset will be defined using diagnosis codes (ICD-9-CM and ICD-10-CM) and procedure codes (ICD-9-CM and ICD-10-PCS). Published algorithms will be used whenever possible. Examples of published algorithms utilized in the past include:

- CMS chronic condition categories: <https://www.ccwdata.org/web/guest/condition-categories>
- Quan, H., Sundararajan, V., Halfon, P., Fong, A., Burnand, B., Luthi, J. C., ... & Ghali, W. A. (2005). Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care*, 1130-1139. <http://www.ncbi.nlm.nih.gov/pubmed/16224307>
- Elixhauser, A., Steiner, C., Harris, D. R., & Coffey, R. M. (1998). Comorbidity measures for use with administrative data. *Medical Care*, 36(1), 8-27. <http://www.ncbi.nlm.nih.gov/pubmed/9431328>

These algorithms will be updated as necessary to account for coding changes since publication. And, if not provided, mapping of diagnosis codes from ICD-9-CM to ICD-10-CM and mapping of procedure codes from ICD-9-CM to ICD-10-PCS will be done using the general equivalence mappings provided by Centers for Medicare & Medicaid Services (CMS):

- Diagnosis code crosswalk: <http://www.cms.gov/Medicare/Coding/ICD10/2014-ICD-10-CM-and-GEMs.html>

- Procedure code crosswalk: <http://www.cms.gov/Medicare/Coding/ICD10/2014-ICD-10-PCS.html>

Algorithms used to identify specific medications dispensed will be defined using different drug identification coding systems in use by study sites. These systems could include:

- NDC codes [from RxNav, a browser for drug information available from the U.S. National Library of Medicine]
- DIN codes [from Health Canada drug product database]
- ATC codes [from WHO Collaborating Centre for Drug Statistics Methodology]

#### **11.7.3.4.2. Sites**

Participating study sites will:

- Extract, transform, and load (ETL) data into a physical instance of an adapted PCORnet Common Data Model. Sites will document the mapping from the EHR to the Common Data Model.
- Install PopMedNet
- Refresh the Cohort DataMart on a biweekly basis
- Execute data characterization and test queries after each refresh and on an as-needed basis.

Site study coordinators will be required to complete pre-screening logs on all potential study participants meeting minimum eligibility requirements (age >40, Type 2 diabetes, established cardiovascular disease) identified via any mechanism (i.e., reviewing lists of scheduled office patients, reviewing lists of recently discharged diabetes patients, EHR-facilitated algorithm). Pre-screening logs will capture the following information:

- Pre-screening number
- Pre-screening date
- Inclusion criteria not met
- Exclusion criteria met
- Other criteria

Site study coordinators will complete a screening survey which will describe the site's current process for screening. A description of screening barriers will be included.

## 11.7.4. DATA ANALYSIS

### 11.7.4.1. Sample Size Expectations

The objectives of this ancillary study are exploratory (not confirmatory) in nature and not intended to be sufficiently powered to confirm a pre-determined level of sensitivity and specificity. The number of sites and subjects that will participate in the ancillary study depends upon the outcome of the site EHR capabilities assessment described in Section 11.7.3.2 (Site Selection). Five study sites recruiting 12-15 subjects each would enable a descriptive assessment of Objectives 1 and 2, whilst, if feasible, 500-1000 subjects at EHR-enabled sites would permit greater precision to be achieved in the assessment of Objective 3.

### 11.7.4.2. Objective 1: Assess the Barriers to Using as EHR-Generated List of Patients to Facilitate Trial Enrollment

Because any survey administered for this objective will be a site-level survey, analysis of the survey data will be performed across all sites. For quantities of interest, frequencies with percentages for categorical measures and means with standard deviations for continuous measures will be presented.

### 11.7.4.3. General Analytic Approach for Objective 1 and Objective 2

The goals of both Objective 2 and Objective 3 involve evaluating the performance of algorithms that map EHR-based data into concepts present in the clinical trial dataset. The actual measures recorded in the clinical trial dataset will be considered the reference standard against which these algorithm-based measures are compared.

**Table 4 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Categorical variables**

New measure (EHR Ancillary Study data)	Reference standard (Clinical trial data)	
	Condition present	Condition absent
Condition present	True positive (TP)	False positive (FP)
Condition absent	False negative (FN)	True negative (TN)

For categorical variables, estimated performance metrics will be based on the 2x2 cross-tabulation of values in the EHR Ancillary Study dataset with values in the clinical trial dataset (Table 4) and include:

- Overall agreement =  $(TP + TN) / (TP + FP + FN + TN)$
- Sensitivity =  $TP / (TP + FN)$

- Specificity =  $TN / (FP + TN)$
- Positive predictive value =  $TP / (TP + FP)$
- Negative predictive value =  $TN / (FN + TN)$
- Accuracy or efficiency =  $(TP + TN) / (TP + TN + FP + FN)$

For dichotomous measures, each of these proportions is immediately calculable. For measures having more than two levels, multiple dichotomous measures will be created in order to calculate these proportions. Confidence intervals (95%) will be reported around these quantities. (See [Table 5](#) as an example).

**Table 5 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Categorical variables**

Measure	Overall agreement (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Measure 1	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
Measure 2	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
.....	.....	.....	.....	.....	.....

Reported on 0–100 scale

For continuous measures, bias will be calculated as the difference between values in the EHR Ancillary Study dataset and values in the clinical trial dataset. The mean and standard deviation of the bias along with a 95% confidence interval will be reported. In Bland-Altman analyses of agreement between continuous measures, the standard deviation of the bias is referred to as the precision, while the 95% confidence interval is referred to as the limit of agreement. (See [Table 6](#) as an example).

**Table 6 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Continuous variables**

Measure	Bias	
	Mean (SD)	95% (CI)
Measure 1	xx.x	xx.x
Measure 2	xx.x	xx.x
.....	.....	.....

Due to the nature of EHR data, it is expected that there will be systematic differences between sites with respect to coding of clinical concepts. All performance metrics will therefore initially be calculated by site. These site-specific results may be best reported graphically.

There is also interest in an assessment of algorithm performance across all sites. Hierarchical models will be used to combine data from all sites and estimate performance at the “average” site. To estimate proportions (e.g. for overall agreement, sensitivity, specificity, etc. associated with categorical measures), models will be specified as:

$$\begin{aligned} \text{logit}(E(y)) &= \beta_0 + \gamma_{0,j} \\ \gamma_{0,j} &\sim N(0, s^2) \end{aligned}$$

where sites are indexed by  $j$ . The value of the proportion at the average site—when  $\gamma_0=0$ —is  $[1 + \exp(-\beta_0)]^{-1}$ . Patients included in the estimation of each model vary by performance metric and reflect the definitions above. As an example, consider positive predictive value. To estimate the positive predictive value of an algorithm, only subjects with true positive value and false positive values will be included. True positives will be assigned  $Y=1$  and false positive will be assigned  $Y=0$ .

To estimate means (e.g. for bias associated with continuous variables), the model will be specified as:

$$\begin{aligned} E(y) &= \beta_0 + \gamma_{0,j} \\ \gamma_{0,j} &\sim N(0, s^2) \end{aligned}$$

The value of the mean at the average site is  $\beta_0$ .

For all models, we will assess site heterogeneity by testing if  $s^2=0$ .

#### **11.7.4.4. Objective 2: Evaluate the Fitness of EHR Data for Use in Populating the Baseline Characteristics in the eCRF**

Algorithms will be defined to map EHR-based data in the Study Data Mart to specific concepts in the EHR Ancillary Study dataset that parallel concepts in the clinical trial dataset. For Objective 2, the performance of algorithms used to identify baseline characteristics will be evaluated. The baseline characteristic measures recorded in the clinical trial dataset will be considered the reference standard against which these algorithm-based measures are compared.

#### **11.7.4.5. Objective 3: Explore the Use of EHR Data to Find Events of Interest During Trial Follow-up**

Algorithms will be defined to map EHR-based data in the Study Data Mart to specific concepts in the EHR Ancillary Study dataset that parallel concepts in the clinical trial dataset. For Objective 3, the performance of algorithms used to identify trial events will be evaluated. These algorithms will be evaluated against both the adjudicated events recorded in the clinical trial dataset and the identified potential events in the eCRF. For each event, estimates of sensitivity and positive predictive value (described in Section [11.7.4.3](#)) will be calculated and presented with 95% confidence intervals.

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## **11.8. Appendix 8: Country Specific Requirements**



## **11.9. Appendix 9: Protocol Amendment Changes**

### **11.9.1. Changes Resulting from Protocol Amendment 1**

This amendment is applicable to all participating countries.

#### **Summary of Changes**

1. Correction of typographical error in Exclusion criterion 7.
2. Clarification wording added to the description of when subjects should have telephone follow-up after discontinuing investigational product (IP). Subjects should have the telephone follow-up  $5 \pm 1$  weeks after their last dose of IP whether they had continued IP through to the Final study visit, or discontinued before the Final study visit.
3. Time and Event Table modified to add adverse event checking (SAE, AEs of special interest, AEs leading to IP discontinuation) to dose adjustment visits, and to correct footnote assignment/typographical errors.
4. Revision of terminology used to describe unstable angina events referred for CEC adjudication to correctly reflect review process to be adopted by CEC.
5. Addition of Country Specific Requirements appendix (Appendix 8).

#### **List of Specific Changes**

Section 4.2, Exclusion criteria; criterion 7, fourth sentence.

*Original text:*

Women who have developed spontaneous secondary amenorrhoea of 12 months or more where post-menopausal status is in doubt, a blood sample where FSH >40MU/ml and oestrodiol <40 pg/mL (<14 pmol/L) are simultaneously measured will be considered confirmatory.

*Amended text:*

Women who have developed spontaneous secondary amenorrhoea of 12 months or more where post-menopausal status is in doubt, a blood sample where FSH >40MU/ml and oestrodiol <40 pg/mL (<14~~0~~ pmol/L) are simultaneously measured will be considered confirmatory.

Section 4.5 Procedures for Subject Follow-up*Original text:*

As described in Section 4.4, subjects who permanently discontinue investigational product will be asked to attend the clinic as soon as possible. They will continue in the study for follow-up. They will be asked to return to clinic according to the 8 monthly visit schedule and in addition be contacted by telephone at a time corresponding to the 4-monthly visit they would have otherwise made to replenish study medication supply. If instead of these interim telephone contacts the subject prefers to attend clinic every 4 months as originally scheduled that is an acceptable alternative.

*Amended text:*

As described in Section 4.4, subjects who permanently discontinue investigational product will be asked to attend the clinic as soon as possible. They will continue in the study for follow-up. ***Five weeks ( $\pm 1$  week) after discontinuation of investigational product, subjects will be contacted for a follow-up by telephone.*** They will be asked to return to clinic according to the 8 monthly visit schedule and in addition be contacted by telephone at a time corresponding to the 4-monthly visit they would have otherwise made to replenish study medication supply. If instead of these interim telephone contacts the subject prefers to attend clinic every 4 months as originally scheduled that is an acceptable alternative.

Table 1 Time and Events Table

*Original text:*

Procedures <sup>1,2</sup>	Screening <sup>2</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post and.)	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	Post-Study Follow up Phone Call 5 ± 1 weeks after last IP dose
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X		X	X	X

1. Subjects who discontinue investigational product should be handled as described in Section 4.4.

11. Study drug dispensing not performed at final visit, compliance check not performed at Screening.

*Amended text:*

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post rand.)	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	<del>Post-Study</del> Follow up Phone Call 5 ± 1 weeks after last IP dose
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X	X	X	X	X

1. Subjects who discontinue investigational product should be handled as described in Section 4.4 **and Section 4.5**.

11. Study drug dispensing not performed at final visit, compliance check not performed at **Randomisation**.

Section 6.2.1 Cardiovascular Events*Original text:*

The CEC will review and adjudicate the following clinical events:

- Myocardial infarction
- Stroke
- Unstable angina requiring revascularization
- Hospitalization for heart failure
- Sudden cardiac death
- TIA
- In addition, all clinical events submitted for adjudication and all other SAEs with a fatal outcome will be reviewed and adjudicated to classify the cause of death as cardiovascular or non-cardiovascular.

*Amended text:*

The CEC will review and adjudicate the following clinical events:

- Myocardial infarction
- Stroke
- ***Unstable angina requiring hospitalization***
- Hospitalization for heart failure
- Sudden cardiac death
- TIA
- In addition, all clinical events submitted for adjudication and all other SAEs with a fatal outcome will be reviewed and adjudicated to classify the cause of death as cardiovascular or non-cardiovascular.

Appendix 8 – Country Specific Requirements

Appendix 8 added (not in original text). This is a blank page headed “11.8. Appendix 8: Country Specific Requirements” to serve as a placeholder to be replaced by each participating GSK Country Medical Department with the appropriate text upon receipt of the protocol and before they distribute it further within their country.

### 11.9.2. Changes Resulting from Protocol Amendment 2

This amendment is applicable to all participating countries (with the exception of item 8 below which is specific to Mexico).

#### Summary of Changes

1. Amendment to indicate that the study should be considered Phase III in countries where albiglutide has not been granted marketing authorisation and Phase IV in countries where it has been.
2. Update to list of protocol authors.
3. Update to Sponsor Medical Monitor Contact Information.
4. Correction of terminology in Treatment Assignment section.
5. Removal of discrepancy between inclusion criterion 4 which wrongly indicates a negative **serum** pregnancy test is required to exclude pregnancy and the Time & Event table (Section 6), Section 6.2.6 Clinical Laboratory Assessments, the model consent form and the Study Reference Manual (which all correctly indicate that the requirement is for a negative **urine** test).
6. Time and Event Table 1 re-formatted as some investigators had found it confusing.
7. Addition of a Time and Event table of assessments to be performed for patients permanently discontinuing IP (Table 2). The visits and telephone contact to be performed for patients discontinuing IP had been described in text previously but an additional tabular format was recommended to aid investigators.
8. Mexican Ministry of Health requirement to report events referred to CEC by Mexican investigators to also be reported to the Ministry as SAEs.
9. Addition of requirement to record lipid results if they are available from subjects' routine clinical care outside of the trial.
10. Clarify that TRIM-D should not be assessed at Baseline in subjects whose diabetes is treated by diet and exercise alone.
11. Corrections to Data Analysis and Statistical Considerations Section to make it more terminologically correct.
12. Simplification of description of information in Section 8.3.6.4 Other Safety Analyses to properly reflect the planned reports.
13. Correction of typographical error in spelling of spermicide.
14. Correction of recipient of faxed SAE reports if the electronic CRF is unavailable.

## List of Specific Changes

### Title Page

*Original text:*

Development Phase: IV

*Amended text:*

Development Phase: **III/IV**

*Original text:*

**Author (s):** The protocol was developed by the members of the Executive Committee in conjunction with Duke Clinical Research Institute and the Sponsor.

The following individuals provided substantial input during protocol development:

**Non-sponsor:** PPD [REDACTED] (Executive Committee Co-Chair);  
PPD [REDACTED] (Executive Committee Co-Chair); PPD [REDACTED]

**Sponsor:** PPD [REDACTED]  
PPD [REDACTED]

*Amended text:*

**Author (s):** The protocol was developed by the members of the Executive Committee in conjunction with Duke Clinical Research Institute and the Sponsor.

The following individuals provided substantial input during protocol development:

**Non-sponsor:** PPD [REDACTED]  
PPD [REDACTED] (Executive Committee Co-Chair); PPD [REDACTED]  
PPD [REDACTED] (Executive Committee Co-Chair); PPD [REDACTED]

**Sponsor:** PPD [REDACTED]  
PPD [REDACTED]

Sponsor Information Page, Sponsor Medical Monitor Contact Information

*Original text:*

**Sponsor Medical Monitor Contact Information:**

Dr PPD [REDACTED]  
2301 Renaissance Boulevard  
REN0410

King of Prussia, Pennsylvania 19406, USA

Email: PPD

Fax: PPD

Telephone number: Office: PPD

Cell: PPD

Out of hours: PPD

*Amended text:*

**Sponsor Medical Monitor Contact Information:**

Dr PPD

2301 Renaissance Boulevard

REN0410

King of Prussia, Pennsylvania 19406, USA

Email: PPD

Fax: PPD

Telephone number: Office: PPD

Cell: PPD

Out of hours: PPD

List of Abbreviations

*Original text:*

Did not include the abbreviations added in amendment.

*Amended text:*

HDLc	high density lipoprotein cholesterol
LDLc	low density lipoprotein cholesterol
Tg	triglycerides
TC	total cholesterol

Section 3.1 Overall Design, first paragraph

*Original text:*

This is a Phase IV, randomised, double blind, parallel-group, placebo-controlled, multicentre study.

*Amended text:*

This is a ~~Phase IV~~, randomised, double blind, parallel-group, placebo-controlled, multicentre study. ***In countries where marketing authorization has been granted to albiglutide for the treatment of type 2 diabetes it is classified as a Phase IV study, elsewhere it should be considered to be a Phase III study.***

Section 4.1 Inclusion Criteria; criterion 4, first sentence

*Original text:*

Female: subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test for females of reproductive potential only), not breastfeeding, and at least one of the following conditions applies:

*Amended text:*

Female: subject is eligible to participate if she is not pregnant (as confirmed by a negative ~~serum~~ ***urine*** human chorionic gonadotrophin (hCG) test for females of reproductive potential only), not breastfeeding, and at least one of the following conditions applies:

Section 5.2 Treatment Assignment; final paragraph

*Original text:*

Blinded study centre personnel will receive a randomisation notification indicating only the unique subject identifier and the date and time of randomisation. Each subject number will be a unique identifier. Once a subject number has been assigned, the number will not be reused even if the subject withdraws before receiving any investigational product. Details of the treatment assignment process are contained in the SRM.

*Amended text:*

Blinded study centre personnel will receive a randomisation notification indicating ~~only~~ the unique subject identifier (***randomisation number***) and the date and time of



randomisation. Each ***randomisation*** subject number will be a unique identifier. Once a ***randomisation*** subject number has been assigned, the number will not be reused even if the subject withdraws before receiving any investigational product. Details of the treatment assignment process are contained in the SRM.

Table 1 Time and Events Table

Original text:

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post rand.)	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	Follow up Phone Call 5 ± 1 weeks after last IP dose
Written informed consent	X							
Review of Inc/excl criteria	X	X						
Demography & directed medical history	X							
Assessment of MACE and micro-vascular events				X		X	X	
HbA1c	X <sup>5</sup>			X		X	X	
Serum creatinine (eGFR)	X <sup>5</sup>					X	X	
Liver Function Tests <sup>6</sup>		X				X	X	
Genetic sampling <sup>7</sup>		X						
Patient reported outcomes questionnaires <sup>8</sup>		X				X	X	
Key concomitant non-diabetes medication		X		X		X	X	X
Diabetes medication		X		X		X	X	X
Study drug reminder			X	X	X	X		
Physical examination <sup>9</sup>		X				X	X	
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X	X	X	X	X
Pregnancy test <sup>10</sup>	X	X						
Study drug dispense/compliance <sup>11</sup>		X		X	X	X	X	

- Subjects who discontinue investigational product should be handled as described in Section 4.4 and Section 4.5.
- Assessments per the Month 4 visit will alternate with those per the Month 8 visit throughout the study i.e., assessments at months 4, 12, 20 etc will be per Month 4; those at month 8, 16, 24 etc. will be per Month 8.
- Screening and Randomisation can occur at the same visit if all eligibility information is available. If Screening and Randomisation occur at the same visit assessments should not be duplicated.
- Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.
- HbA1c and creatinine assessed using local laboratories at Screening visit and measured no more than 6 months prior to randomisation. If HbA1c or creatinine have not been assessed in the previous 6 months assessments to be performed via a central laboratory and results available prior to randomization. The investigator has the discretion to repeat

- screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.
6. Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT. Blood samples for LFTs at randomization must be collected prior to the first dose of investigational product.
  7. Informed consent for genetic research must be obtained before collecting a sample. Genetics sample can be collected at any time after genetic consent has been obtained and the subject has been randomised.
  8. TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
  9. See Section 6.2.7.
  10. Only applies to women of child bearing potential. At screening perform urine pregnancy test. If positive, send serum sample to the central laboratory for confirmation. At Randomisation perform a urine pregnancy test. If result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised. If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. See Section 6.2.6.
  11. Study drug dispensing not performed at final visit, compliance check not performed at Randomisation

*Amended text:*

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post rand.)	Clinic Visit Month 4 ± 18 days then every 4 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	Follow up Phone Call 5 ± 1 weeks after last IP dose
Written informed consent	X							
Review of Inc/excl criteria	X	X						
Demography & directed medical history	X							
Assessment of MACE and micro-vascular events				X		X	X	
HbA1c	X <sup>5</sup>			X		X	X	
Serum creatinine (eGFR)	X <sup>5</sup>			X (alternate visits) 2		X	X	
Liver Function Tests (LFTs) <sup>6</sup>		X		X (alternate visits) 2		X	X	
<b>Record available information on most recent lipid assessment<sup>7</sup></b>		X		X (annually)			X	
Genetic sampling <sup>7,8</sup>		X						
Patient reported outcomes questionnaires <sup>8,9</sup>		X <sup>10</sup>		X (alternate visits) 2		X	X	
Key concomitant non-diabetes medication		X		X		X	X	X

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post rand.)	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit* (or early withdrawal)	Follow up Phone Call 5 ± 1 weeks after last IP dose
Diabetes medication		X		X		X	X	X
Study drug reminder			X	X	X	X		
Physical examination <sup>9,11</sup>		X		X (alternate visits) 2		X	X	
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X	X	X	X	X
Pregnancy test <sup>10,12</sup>	X	X						
Study drug dispense/compliance <sup>11,13</sup>		X		X	X	X	X	

- Subjects who discontinue investigational product should be handled as described in Section 4.4 and Section 4.5 **and in Table 2.**
- ~~Assessments per the Month 4 visit will alternate with those per the Month 8 visit throughout the study i.e., assessments at months 4, 12, 20 etc will be per Month 4; those at month 8, 16, 24 etc. will be per Month 8.~~ **Assessments at month 8, 16, 24 etc. will include patient reported outcomes questionnaires, serum creatinine (eGFR), liver function tests and physical examination. Those at months 4, 12, 20 etc do not.**
- Screening and Randomisation can occur at the same visit if all eligibility information is available. If Screening and Randomisation occur at the same visit assessments should not be duplicated.
- Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.
- HbA1c and creatinine assessed using local laboratories at Screening visit and measured no more than 6 months prior to randomisation. If HbA1c or creatinine have not been assessed in the previous 6 months assessments to be performed via a central laboratory and results available prior to randomization. The investigator has the discretion to repeat screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.
- Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT. Blood samples for LFTs at randomization must be collected prior to the first dose of investigational product.
- Lipid values (TC, LDLc, HDLc, Tg) to be recorded as available from routine clinical care at baseline and annually thereafter. If results are unavailable, lipid tests are not to be performed for the study.**
- Informed consent for genetic research must be obtained before collecting a sample. ~~Genetics sample~~ **This** can be collected at any time after genetic consent has been obtained and ~~the subject has been randomised~~ **randomisation has occurred.**
- TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
- TRIM-D is not required for subjects whose diabetes is treated by diet and exercise alone at Baseline.
- See Section 6.2.7.
- Only applies to women of child bearing potential. At screening perform urine pregnancy test. If positive, send serum sample to the central laboratory for confirmation. At Randomisation perform a urine pregnancy test. If result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised. If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. See Section 6.2.6.
- Study drug dispensing not performed at final visit, compliance check not performed at Randomisation

Section 6 Study Assessments and Procedures; insertion of the following table after Table 1

**Table 7 Time and Events Table for Subjects Who Permanently Discontinue IP Prior to the End of the Study**

Procedures	Clinic visit as soon after permanent discontinuation of IP as possible	Phone Call 5 ± 1 week after last IP dose	Continue contact schedule established at randomisation 4 monthly ± 1 month. <b>Telephone</b> <sup>1,2</sup>	Continue contact schedule established at randomisation 4 monthly ± 1 month. <b>Clinic visit</b> <sup>1,3</sup>	Final study clinic visit <sup>4</sup>
Assessment of MACE and micro-vascular events	<b>X</b>		<b>X</b>	<b>X</b>	<b>X</b>
HbA1c	<b>X</b>			<b>X</b>	<b>X</b>
Serum creatinine (eGFR)	<b>X</b>			<b>X</b>	<b>X</b>
Liver Function Tests (LFTs) <sup>5</sup>	<b>X</b>			<b>X</b>	<b>X</b>
Record available information on most recent lipid assessment <sup>6</sup>	<b>X</b>		<b>X (annually)</b>	<b>X (annually)</b>	<b>X</b>
Patient reported outcomes questionnaire <sup>7</sup>	<b>X</b>				
Key concomitant non-diabetes medication	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
Diabetes medication	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
Physical examination <sup>8</sup>	<b>X</b>			<b>X</b>	<b>X</b>
AEs leading to IP discontinuation	<b>X</b>				
SAEs, AEs of special interest,	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
Study drug compliance	<b>X</b>				

1. After subjects permanently discontinue IP, follow-up should continue on the 4-monthly schedule established at randomisation.
2. Where a subject would have been scheduled to attend clinic at months 4, 12, 20, 28 etc after randomisation, a telephone contact will be performed instead (with assessments as shown above).
3. Where a subject would have been scheduled to attend clinic at months 8, 16, 24, 32 etc after randomisation, a clinic visit will be performed (with assessments as shown above). If a subject who has permanently discontinued IP is unable to attend clinic then they will be contacted by telephone instead and the telephone contact assessments will be performed.
4. Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.
5. Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT.
6. Lipid values (TC, LDLc, HDLc, Tg) to be recorded as available from routine clinical care annually. If results are unavailable, lipids tests are not to be performed for the study.
7. TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
8. See Section 6.2.7.

Section 6.2.1 Cardiovascular Events; footnote added to end of first sentence.*Original text:*

Events referred to the CEC by the investigator as potential endpoints or transient ischemic attacks (TIAs) will not be collected or reported as SAEs, regardless of the adjudication outcome (Section 6.2.2).

*Amended text:*

Events referred to the CEC by the investigator as potential endpoints or transient ischemic attacks (TIAs) will not be collected or reported as SAEs, regardless of the adjudication outcome (Section 6.2.2).<sup>1</sup>

## Footnote:

***<sup>1</sup> There is one exception to this statement. Per requirement of the Mexican Ministry of Health, all events referred to the CEC by Mexican investigators will also be submitted as SAEs to the Mexican Ministry of Health.***

Section 6.2.6 Clinical Laboratory Assessments; text to be inserted at end of sub-section***Lipids***

***Where serum lipid tests have been performed as part of the subject's routine clinical care (i.e. not as a study procedure) the most recent results should be recorded at baseline and annually thereafter. The lipid parameters to be recorded are total cholesterol (TC), low density lipoprotein cholesterol (LDLc), high density lipoprotein (HDLc) and triglycerides (Tg).***

***If any or all of these results are not already available from the subject's records then separate lipid tests should not be performed solely for the study.***

## Section 6.3.1.1. Treatment Related Impact Measure – Diabetes (TRIM-D)

*Original Text:*

In order to evaluate satisfaction with treatment and to compare satisfaction across treatment groups, the TRIM-D questionnaire will be self administered by all subjects at baseline and at each 8 month visit (and, to the extent possible, at the time of study completion or withdrawal from the study).

*Amended Text:*

In order to evaluate satisfaction with treatment and to compare satisfaction across treatment groups, the TRIM-D questionnaire will be self administered by all subjects at baseline (except for subjects whose diabetes is treated by diet and exercise alone) and all subjects at each 8 month visit (and, to the extent possible, at the time of study completion or withdrawal from the study).

Section 8.3.3.1 Primary Comparisons of Interest, second sentence*Original text:*

The primary endpoint will be the time to the first occurrence of MACE over the full duration of the study. A p-value for the primary endpoint will be calculated from a Cox regression model with treatment group as the only covariate for the hypotheses described in Section 8.1.

*Amended text:*

The primary endpoint will be the time to the first occurrence of MACE over the full duration of the study. A p-value for the primary endpoint will be calculated from a Cox **Proportional Hazards (PH)** regression model with treatment group as the only covariate for the hypotheses described in Section 8.1.

Section 8.3.3.2. Other Comparisons of Interest, insertion of two new sentences:*Original text:*

For other analyses incidence rates will be presented for binary data and summary statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous data. Furthermore, summary statistics of change from baseline for HbA1c will be presented along with percent of subjects within ranges of clinical interest (e.g., HbA1c < 7.0%).

*Amended text:*

For other analyses incidence rates will be presented for binary data and summary statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous data. ***Time to event endpoints will be evaluated via the p-value from a Cox PH regression model with treatment as the only covariate.*** Furthermore, summary statistics of change from baseline for HbA1c will be presented along with percent of subjects within ranges of clinical interest (e.g., HbA1c < 7.0%). ***Available lipid data will be summarized for descriptive purposes.***

Section 8.3.6.2. Secondary Endpoint Analysis*Original text:*

- Composite of the proportion of those achieving good control (HbA1c ≤ 7.0%) AND no severe hypoglycaemic incidents AND weight gain <5% at the end of the study would be evaluated utilize nonparametric, covariance-adjusted, extended Mantel-Haenszel tests. Additional analysis will be provided for scheduled visits. Nominal p-values and 95% CIs will be presented for these visits. Time to introduction of prandial insulin in those on basal insulin ± orals anti-hyperglycemic drugs at baseline will be analyzed using PH model / log-rank test and KM method similar to the primary endpoint.

- Composite of microvascular events will be analyzed using a proportional Cox regression model / log-rank test and KM method similar to the primary endpoint.

*Amended text:*

- Composite of the proportion of those achieving good control ( $HbA1c \leq 7.0\%$ ) AND no severe hypoglycaemic incidents AND weight gain  $<5\%$  at the end of the study would be evaluated utilize nonparametric, covariance-adjusted, extended Mantel-Haenszel tests. Additional analysis will be provided for scheduled visits. Nominal p-values and 95% CIs will be presented for these visits. Time to introduction of prandial insulin in those on basal insulin  $\pm$  orals anti-hyperglycemic drugs at baseline will be analyzed using **a Cox PH** model ~~/log-rank test~~ and KM method similar to the primary endpoint.
- Composite of microvascular events will be analyzed using a proportional Cox regression model ~~/log-rank test~~ and KM method similar to the primary endpoint.

Section 8.3.6.4. Other Safety Analyses, paragraphs 3, 4 and 5.

*Original text:*

For SAEs, AEs leading to withdrawal and AEs of special interest occurring after discontinuation of investigational product, the number and percentage of subjects, total number of events, incidence density and event rate will be presented by treatment group and overall at the SOC, High Level Term and Preferred Term (PT) level. Relative Risk for each event and its 95% CI will also be presented. The time to first occurrence of the specific events and the time of the event with respect to the preceding dose of study medication will be summarized.

All cause mortality will be summarized by treatment group and analyzed using PH model similarly as the-primary endpoint.

All events sent to CEC (including TIAs) will be grouped by type based on the standard MedDRA queries that correspond to cardiovascular and cerebrovascular events. Adjudication results will be summarized by event type and treatment group. A by subject listing of these events will be generated. The listing will include seriousness, severity, whether event is a reason for early study drug discontinuation or study withdrawal, and adjudication results.

Pancreatitis events will be adjudicated by the independent Pancreatitis Adjudication Committee. The information for investigator reported pancreatitis events and its adjudication results will be provided.

*Amended text:*

For SAEs, AEs leading to **permanent IP** withdrawal and AEs of special interest ~~occurring after discontinuation of investigational product~~, the number and percentage of subjects, total number of events, **and** incidence density ~~and event rate~~ will be presented by treatment group and overall at the SOC, ~~High Level Term~~ and Preferred Term (PT) level. Relative Risk ~~for each event~~ and its 95% CI ~~will~~**may** also be presented **on a**



**targeted basis.** The time to first occurrence of the specific events ~~and the time of the event with respect to the preceding dose of study medication~~ will be summarized.

All cause mortality will be summarized by treatment group and analyzed using **a Cox PH** model similarly as the primary endpoint.

All events sent to CEC (including TIAs) will be **summarized**. ~~grouped by type based on the standard MedDRA queries that correspond to cardiovascular and cerebrovascular events. Adjudication results will be summarized by event type and treatment group. A by subject listing of these events will be generated. The listing will include seriousness, severity, whether event is a reason for early study drug discontinuation or study withdrawal, and adjudication results.~~

Pancreatitis events will be adjudicated by the independent Pancreatitis Adjudication Committee. The information for investigator reported pancreatitis events and its adjudication results will be **summarized**~~provided~~.

#### Section 8.3.6.5 Value Evidence and Outcomes Analyses

##### Original Text:

TRIM-D total score and score for each domain will be summarized descriptively by treatment group and scheduled visit. Score changes from baseline will be compared between treatments for each visit by ANCOVA an model.

##### Amended Text:

TRIM-D total score and score for each domain will be summarized descriptively by treatment group and scheduled visit. Score changes from baseline will be compared between treatments for each visit by an ANCOVA an model.

#### Section 11.2 Appendix 2: GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP), final listed item

##### Original text:

8. Male condom **combined with a female** diaphragm, with or without a vaginal spermicide (foam, gel, film, cream, or suppository). In the UK it is a country-specific requirement of the regulatory authority (Medicines and Healthcare Products Regulatory Agency) that a vaginal spermicide be used.

##### Amended text:

8. Male condom **combined with a female** diaphragm, with or without a vaginal spermicide (foam, gel, film, cream, or suppository). In the UK it is a country-specific

requirement of the regulatory authority (Medicines and Healthcare Products Regulatory Agency) that a vaginal ~~spermicide~~ **spermicide** be used.

Section 11.5.5 Reporting of SAEs to GSK, edit to second bullet, insertion of new third bullet

*Original text:*

- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor or the SAE coordinator

*Amended text:*

- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the ~~Medical Monitor or the SAE coordinator~~ **safety designee as detailed in the Study Reference Manual**
- ***The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.***

## TITLE PAGE

**Division:** Worldwide Development

**Information Type:** Protocol Amendment

<b>Title:</b>	A long term, randomised, double blind, placebo-controlled study to determine the effect of albiglutide, when added to standard blood glucose lowering therapies, on major cardiovascular events in patients with Type 2 diabetes mellitus  Harmony Outcomes Trial
---------------	---

**Compound Number:** GSK716155

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**Effective Date:** 24-NOV-2014

**Protocol Amendment Number:** 1

**Author (s):** The protocol was developed by the members of the Executive Committee in conjunction with Duke Clinical Research Institute and the Sponsor.

The following individuals provided substantial input during protocol development:

**Non-sponsor:** PPD (Executive Committee Co-Chair);  
PPD (Executive Committee Co-Chair); PPD

**Sponsor:** PPD  
PPD

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Clarification added regarding follow-up after discontinuation of investigational product. Addition of safety assessment to dose adjustment visits. Addition of Country Specific Requirements appendix. Correction of typographical errors and inconsistent terminology.		

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**SPONSOR SIGNATORY**

PPD



---

Dr Salim Janmohamed BSc MBBS (Hons) FRCP  
Project Physician Leader - albiglutide

24 NOVEMBER 2014

---

**Date**

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**Regulatory Agency Identifying Number(s):**

Investigational New Drug (IND) Number: IND65177  
European Drug Regulatory Authorities Clinical Trials (EudraCT) No. 2014-001824-32.

**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

For protocol number GLP116174

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Signature:	Date

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## LIST OF ABBREVIATIONS

ACCF	American College of Cardiology Foundation
ADA	American Diabetes Association
AE	adverse event
AHA	American Heart Association
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANCOVA	analysis of covariance
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BI	baseline basal insulin population
BMI	body mass index
bpm	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEC	Cardiovascular Endpoint Committee
CI	confidence interval
CPK	creatine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
DCRI	Duke Clinical Research Institute
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EHR	electronic health record
ESC	European Society of Cardiology
FDA	US Food and Drug Administration
FRP	females of reproductive potential
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GSK	GlaxoSmithKline
HbA1c	glycated haemoglobin
hCG	human chorionic gonadotrophin
HLA	human leukocyte antigen
HRT	hormone replacement therapy
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normal range
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	Interactive Voice Response System
KM	Kaplan-Meier

LDH	lactate dehydrogenase
LFT	liver function test
MACE	major adverse cardiovascular event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MSDS	Material Safety Data Sheet
MTC	medullary thyroid cancer
NHLBI	National Heart, Lung and Blood Institute
NI	non-insulin population
PAD	peripheral arterial disease
PD	pharmacodynamics
PHI	Protected Health Information
PK	pharmacokinetics
PP	per protocol
RAP	Reporting Analysis Plan
RR	relative risk
s.c.	subcutaneous
SAE	serious adverse event
SRM	Study Reference Manual
SU	sulfonylureas
TIA	transient ischemic attack
TRIM-D	Treatment Related Impact Measures-D
ULN	upper limit of normal range
WHF	World Heart Federation
WHO	World Health Organization

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## PROTOCOL SUMMARY

### Rationale

Albiglutide is a novel analogue of glucagon-like peptide-1 (GLP-1) with a sufficiently long half-life to permit once a week injection. Albiglutide is licensed for the treatment of type 2 diabetes as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies, including basal insulin. The Food and Drug Administration (FDA) has issued guidance on evaluating cardiovascular risk in new anti-diabetic therapies to treat type 2 diabetes [FDA [Guidance for Industry](#), 2008]. For a premarketing application that contains a meta-analysis of major adverse cardiovascular events (MACE) for which the upper bound of the 95 percent confidence interval for the relative risk is between 1.3 and 1.8, a post-marketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. The MACE meta-analysis of the albiglutide Phase III program (primary endpoint cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina), whilst ruling out an upper bound of the confidence interval for cardiovascular events of 1.8, was not able to rule out (due to a relatively small number of events) a relative risk (RR) upper bound of 1.3. For this reason GlaxoSmithKline (GSK) will conduct this cardiovascular outcome study as a US post-marketing requirement, to evaluate the effect of albiglutide on cardiovascular events in subjects with type 2 diabetes.

### Objectives/Endpoints

Objectives	Endpoints
<b>Primary</b>	
To determine whether albiglutide is non-inferior with respect to MACE when added to glycaemic standard of care versus standard of care alone	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke) [Non-inferiority]</li> </ul>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE [Superiority]<sup>(1 see footnote)</sup></li> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start <sup>(1 see footnote)</sup></li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li>The proportion of subjects achieving glycaemic control (HbA1c ≤ 7.0% at final assessment) with no severe hypoglycaemic incidents and weight gain &lt;5% of body weight <sup>(1 see footnote)</sup></li> <li>The time to first occurrence of a clinically important microvascular event (see Section 6.2.4)</li> <li>Change in glycated haemoglobin (HbA1c)</li> <li>Change in body weight</li> </ul>

Objectives	Endpoints
	<ul style="list-style-type: none"> <li>• Patient reported outcomes from Treatment Related Impact Measures-D (TRIM-D)/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>• All cause mortality</li> <li>• Non-fatal serious adverse events (SAEs)</li> <li>• Adverse events (AEs) leading to discontinuation of investigational product</li> <li>• AE of special interest (see Section 6.2.3)</li> <li>• Change in estimated glomerular filtration rate (eGFR) calculated using Modification of Diet in Renal Disease (MDRD) formula</li> <li>• Change in blood pressure and heart rate</li> </ul>

1. If the primary endpoint meets the criteria for non-inferiority, a multiple comparisons adjustment strategy will be performed for these 3 secondary endpoints as specified in the Section 8.3.5.

## Overall Design

This is a randomised, double blind, parallel group, placebo-controlled study.

## Treatment Arms and Duration

All subjects will receive standard of care for their diabetes and cardiovascular health which can be adjusted by the healthcare professional responsible for the subject during the study according to clinical need and with close adherence to professional society treatment guidelines. The study comparison is thus between albiglutide added to standard of care and standard of care alone. Placebo injections will be used to ensure study assessments are performed without knowledge of treatment assignment. Treatment with albiglutide or placebo will be randomly allocated in a 1:1 ratio. The starting dose of albiglutide is 30 mg weekly which may be up-titrated to 50mg weekly if further improvement of glycaemic control is required.

The study will be event driven, i.e. follow up will continue until it is projected that approximately 611 adjudicated MACE events will have occurred. Consequently, the maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate, and is estimated to be between 3 and 5 years.

An Independent Data Monitoring Committee (IDMC) will have study oversight to ensure participant safety and scientific integrity of the data.

## Type and Number of Subjects

A total of 9400 subjects with type 2 diabetes and a previous history of cardiovascular disease and who do not have optimal glycaemic control will be studied.

## Analysis

The study's primary question is whether albiglutide is non-inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. The primary analysis is an Intent-to-Treat (ITT) analysis of the time to the first occurrence of MACE using Cox's Proportional Hazard regression.

## 1. INTRODUCTION

### 1.1. Background

Diabetes affects an estimated 347 million people worldwide, with type 2 diabetes accounting for more than 90% of cases [[WHO](#), 2013]. The primary manifestation of this disease is chronic hyperglycaemia, resulting from resistance to insulin action at a cellular and molecular level and a relative inadequacy in the secretion of endogenous insulin [[American Diabetes Association](#), 2014]. Chronic hyperglycaemia has been firmly established as a key factor in the development of microvascular complications (retinopathy, nephropathy, and neuropathy). Individuals with type 2 diabetes are also at greatly elevated risk of cardiovascular disease.

The management of glycaemia in individuals with type 2 diabetes consists of diet, exercise, and weight reduction together with oral anti-diabetic drug, injectable agents such as GLP-1 receptor agonists or insulin therapy, to achieve near normoglycaemia as reflected by a target HbA1c level of  $\leq 7\%$ , where possible, without significant hypoglycaemia or other adverse effects of treatment. Despite the large number of available therapeutic agents, a high proportion of subjects fail to achieve or maintain target HbA1c levels [[Khunti](#), 2013] owing to the inexorable decline in endogenous insulin production characteristic of the disease, and limitations in existing treatments. New agents with complementary mechanisms (permitting combination use) or more favourable safety profiles are needed to help more subjects achieve glycaemic targets.

GLP-1 is secreted by intestinal L-cells in response to ingestion of food. In a healthy individual, it plays an important role regulating postprandial blood glucose by stimulating glucose-dependent insulin secretion by the pancreas. GLP-1 suppresses glucagon secretion, leading to reduced hepatic glucose output. It also delays gastric emptying time and slows small bowel motility, delaying food absorption and slowing the rate of glucose appearance in the blood. In patients with type 2 diabetes the postprandial rise in endogenous GLP-1 is absent or reduced [[Vilsbøll](#), 2001].

GLP-1 receptor agonists have been developed as anti-hyperglycemic therapy for type 2 diabetes to replace or supplement endogenous GLP-1 in order to increase meal-related insulin secretion, reduce inappropriate glucagon secretion, and slow GI motility. They have demonstrated substantial effectiveness in improving glycaemic control while mitigating the risk of hypoglycaemia and weight gain commonly associated with some of the other treatments for type 2 diabetes [[Stonehouse](#), 2012].

Albiglutide is a novel analogue of GLP-1 generated through a genetic fusion of 2 modified recombinant human GLP-1 molecules linked in tandem to recombinant human albumin. Albiglutide is licensed for the treatment of type 2 diabetes as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies (oral anti-diabetic therapies or basal insulin). It has been granted marketing authorisation by the European Medicines Agency (EMA) (March 2014) and the FDA (April 2014). Details of the clinical trial results can be found in the Investigator Brochure (IB).

## 1.2. Rationale

The FDA has issued guidance on evaluating cardiovascular risk in new anti-diabetic therapies to treat type 2 diabetes [FDA [Guidance for Industry](#), 2008]. For a premarketing application that contains a meta-analysis of MACE, for which the upper bound of the 95 percent confidence interval for the relative risk is between 1.3 and 1.8, a post-marketing trial may be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3.

The MACE + meta-analysis of the albiglutide Phase III program (primary endpoint cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina), whilst ruling out an upper bound of the confidence interval for cardiovascular events of 1.8, was not able to rule out (due to a relatively small number of events) a RR upper bound of 1.3. For this reason GSK will conduct this cardiovascular outcome study as a US post-marketing requirement, to evaluate the effect of albiglutide on cardiovascular events in subjects with type 2 diabetes.

Preclinical studies have provided evidence that GLP-1 receptor stimulation favourably effects endothelial function, recovery from ischemic injury, and myocardial function in animals [reviewed in [Okerson](#), 2012]. Albiglutide reduced infarct size assessed 24 hours after 30 minutes temporary left anterior descending coronary artery occlusion in normoglycaemic rats [[Bao](#), 2011]. GLP-1 infusion has been shown to improve endothelial function in subjects with stable coronary disease [[Nystrom](#), 2004]. In subjects with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, the GLP-1 receptor agonist, exenatide, administered at the time of reperfusion has been reported to increase myocardial salvage [[Lønborg](#), 2012]. In the Phase III studies, small mean increases in heart rate (1 to 2 bpm) and a higher incidence of atrial fibrillation/flutter events were observed with albiglutide. It is difficult to predict whether these preclinical and clinical findings will translate into effect on major cardiovascular events.



## 2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b>	
To determine whether albiglutide is non-inferior with respect to MACE when added to glycaemic standard of care versus standard of care alone	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke) [Non-inferiority]</li> </ul>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE [Superiority]<sup>(1 see footnote)</sup></li> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start <sup>(1 see footnote)</sup></li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li>The proportion of subjects achieving glycaemic control (HbA1c ≤ 7.0% at final assessment) with no severe hypoglycaemic incidents and weight gain &lt;5% of body weight <sup>(1 see footnote)</sup></li> <li>The time to first occurrence of a clinically important microvascular event (see Section 6.2.4)</li> <li>Change in HbA1c</li> <li>Change in body weight</li> <li>Patient reported outcomes from TRIM-D/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>All cause mortality</li> <li>Non-fatal SAEs</li> <li>AEs leading to discontinuation of investigational product</li> <li>AE of special interest (see Section 6.2.3)</li> <li>Change in eGFR calculated using MDRD formula</li> <li>Change in blood pressure and heart rate</li> </ul>
<b>Exploratory</b>	
To evaluate patient reported experience of diabetes treatment	<ul style="list-style-type: none"> <li>Patient reported outcomes from study specific questionnaire</li> </ul>
To evaluate (at a subset of sites) barriers to using the electronic health record (EHR) to facilitate trial enrolment and the quality of EHR data for use in populating baseline characteristics and identifying events of interest during trial follow-up. <sup>2</sup>	<ul style="list-style-type: none"> <li>Workflow impact of an EHR-generated list of subjects to facilitate trial enrolment.</li> <li>Concordance, sensitivity, specificity, and accuracy of baseline characteristics extracted from the EHR compared with those reported on the electronic case report form (eCRF)<sup>3</sup></li> <li>Concordance, sensitivity, specificity, and accuracy of EHR-identified events compared with study events <sup>3,4</sup></li> <li></li> </ul>

- If the primary endpoint meets the criteria for non-inferiority, a multiple comparisons adjustment strategy will be performed for these 3 secondary endpoints as specified in the Section 8.3.5.
- Details are provided in a separate EHR ancillary study protocol (Appendix 7). Results from this exploratory investigation will be reported separately from the main clinical study report.
- Comparison of EHR identified events with study events will be conducted in the same data subset.
- Analyses to be undertaken after the main trial results are published.

### 3. STUDY DESIGN

#### 3.1. Overall Design

This is a Phase IV, randomised, double blind, parallel-group, placebo-controlled, multicentre study. This study will recruit approximately 9400 subjects with type 2 diabetes and a previous history of cardiovascular disease who are failing to achieve optimal glycaemic control on their current anti-hyperglycaemic regimen. Subjects will be randomised in a 1:1 ratio to albiglutide or albiglutide matching placebo administered once weekly by subcutaneous (s.c.) injection.

All subjects will receive standard of care which can be adjusted by their usual care provider(s) during the study according to clinical need (See Section 3.2). The study comparison is between albiglutide added to standard of care and standard of care alone.

The starting dose of albiglutide will be 30 mg once weekly. If at any stage after 5 weeks of treatment the subject needs to have intensified therapy to improve glycaemic control, the dose of investigational product should be increased before altering the doses of or adding other glucose-lowering medication. This treatment decision will be the responsibility of the investigator. In this case the subject will be called in for an unscheduled visit to increase the dose from 30 mg to 50mg. Subjects randomly assigned to albiglutide matching placebo will also go through the increased dose procedure to maintain study blind. If a subject experiences tolerability issues with the higher, 50mg dose then the investigator may decrease the dose back to 30 mg without the need for an unscheduled visit to supervise down titration. Use of GLP-1 receptor agonists will be prohibited but other glucose-lowering medications permitted, provided they are not contraindicated for the individual subject concerned.

This study is designed with minimal intervention above normal clinical care of subjects with type 2 diabetes, whilst allowing thorough evaluation of cardiovascular and other events of special interest (Section 6.2.3), thus investigating the safety of albiglutide in the typical clinical situation. Sites will employ pre-screening to assess potential subjects for study entry. Screening and randomisation can then occur at the same visit or in close proximity depending on scheduling. Contact with subjects will be every four months after the randomisation visit. HbA1c will be measured at 4 month clinic visits. Serum creatinine and liver function tests (LFTs) will be measured and a targeted physical assessment performed at 8 month clinic visits (Table 1).

The study will be event driven, i.e., follow up will continue until it is projected that approximately 611 adjudicated MACE events will have occurred. Consequently, the maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate, and is estimated to be between 3 and 5 years. If the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years, respectively.

An Executive Committee will be the main decision-making body for the study, in collaboration with the Sponsor (GSK). It is charged with the overall scientific, professional and operational conduct of the study. Amongst other roles pre-specified in

its Charter, the Executive Committee will ensure proper study conduct and conformance to the protocol, consider and agree changes to the protocol based on emerging scientific and/or clinical advances (e.g., new emerging data with other GLP-1 receptor agonists), advise on the selection of study sites and assist in subject recruitment strategies.

An IDMC will have study oversight to ensure participant safety and scientific integrity of the data (Section 9.8), an independent Cardiovascular Endpoint Committee (CEC) blinded to treatment allocation will adjudicate cardiovascular outcome events (Section 6.2.1) and a Pancreatitis Adjudication Committee will adjudicate potential events of pancreatitis.

Subject completion is defined as completion of all periods of the study up to and including any follow-up period.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 1), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

### **3.2. Standard of Care**

Anti-hyperglycaemic and cardiovascular medications will be used at the discretion of the usual care provider(s) (or investigator if also the usual care provider), who will be informed of the patient's enrolment in the trial, the use of blinded trial medication, and that use of GLP-1 receptor agonists (other than the use of randomised albiglutide) is contraindicated during the trial period. Usual care providers will be encouraged to follow the most up to date guidelines for diabetes and cardiovascular care based upon local and institutional practice patterns and any relevant published practice guidelines (e.g., Inzucchi, 2012). Treatment for type 2 diabetes will be captured by name and total daily dose at the time of study visits, while other relevant (cardiovascular) concomitant medications will be collected only as drug classes (see Section 5.6.1).

During the study investigators are expected to monitor patients' type 2 diabetes regimens and communicate with usual care providers, who will be responsible for adjusting their regimen in order to achieve locally-appropriate HbA1c goals. The Executive Committee and National Country Leaders will encourage investigators to follow clinical care practice guidelines published by national and international societies regarding type 2 diabetes over the course of the trial. These practice guideline goals will be individualized, with the understanding that currently applicable glycaemic guidelines may vary among different geographic regions. With adherence to local custom and laws (including privacy regulations such as the Health Insurance Portability and Accountability Act), types of communication may be informal e.g. email or telephone exchanges, to enhance frequency and ease of two-way communication.

Any agent, with the exception of GLP-1 receptor agonists, is acceptable for reaching HbA1c goals. If HbA1c goals are not met following adjustment with oral medications in patients not receiving insulin, an insulin regimen may be initiated. Patients already receiving insulin therapy may up-titrate insulin during the trial if necessary. Patients should be reminded to keep taking their blinded trial medication throughout the course of the trial even in the case after initiation of insulin.

The Executive Committee and National Country Leaders will also monitor the standard of care of management of diabetes and cardiovascular disease. Similar to the management of type 2 diabetes, sites and investigators will be expected to adhere to local clinical practice guidelines. Sites will be provided training on clinical management guidelines to re-enforce standard of care adherence. Information on medications important to management of cardiovascular risk will be captured during study visits. The Executive Committee and National Country Leaders will review on a periodic basis the use of medications for cardiovascular risk prevention to ensure patients are receiving standard of care. If there are unusually low goal attainments for standard of care, site investigators will be advised accordingly.

### **3.3. Discussion of Design**

This study is a clinical outcomes trial required by FDA as a post-marketing requirement to evaluate cardiovascular safety. It will provide important information regarding the cardiovascular safety and metabolic effects of albiglutide treatment of subjects with type 2 diabetes. Sufficient MACE events must be observed during the study to permit the assessment of cardiovascular safety. Consequently, to enter the study subjects must have established cardiovascular disease as well as type 2 diabetes. The study is powered on a predefined number of clinical events, consequently the number of subjects required and study duration may vary from that stated in the protocol.

This will be a double-blind, placebo-controlled study. All subjects will receive placebo or albiglutide in addition to usual standard of care for type 2 diabetes and cardiovascular disease, in order to assess the effect of albiglutide above that of currently available therapies alone.

The primary cardiovascular comparison will be to assess whether albiglutide is non-inferior to placebo with respect to time to first MACE. Missing data may inappropriately bias comparison towards declaring non-inferiority. The longer the duration of a study, the more difficult it is to avoid loss to follow-up and other sources of missing data. The product of the projected duration of this study and the number of subjects to be studied is intended to minimize the risk of missing data whilst still permitting the assessment of the safety of albiglutide to be over an appreciable period of time. Every effort will be made to keep subjects on their assigned study medication according to the protocol. Subjects who stop study medication will be followed throughout the whole study duration. More details about procedures for subject follow-up are provided in Section 4.5.

Phase III studies confirmed the glycaemic efficacy of both 30 mg and 50 mg doses of albiglutide, and both were generally well-tolerated. Although the 30 mg dose was effective at controlling glycaemia for at least 2 years in many subjects with type 2

diabetes, an increase in dose to 50 mg weekly offered additional benefit without significant safety issues (See IB for further details).

### 3.4. Benefit:Risk Assessment

Albiglutide has been evaluated in an international programme of studies involving approximately 9000 subject-years of overall exposure to date (including over 4000 subject-years of exposure to albiglutide). The programme included 8 well-controlled Phase III studies (including one in subjects with concurrent renal impairment), ranging in duration from 32 weeks to 3 years, and using both 30 mg and 50 mg once weekly dosing. This has permitted a thorough assessment of efficacy, safety, and tolerability in a population of subjects with type 2 diabetes that spanned newly diagnosed individuals treated with diet and exercise alone through to subjects on background oral monotherapy, oral dual therapy, oral triple therapy, and basal insulin.

Summaries of findings from both clinical and non-clinical studies conducted with albiglutide can be found in the IB and in the product labelling for those countries where marketing authorisation has been granted. The following section outlines the risk assessment and mitigation strategy for this protocol:

#### 3.4.1. Risk Assessment

The identified and potential risks associated with the use of albiglutide, or the GLP-1 receptor agonist class, as well as the mitigation strategy for key risks of clinical significance are provided below. Please refer to the IB for a thorough summary of the nonclinical and clinical experience with albiglutide as well as the complete Guidance for the Investigator. The risks associated with study comparator, placebo, are also provided below. Subjects will have the AE profile of GLP-1 receptor agonists, and albiglutide in particular, explained to them by the investigator and via the informed consent form.

##### 3.4.1.1. Identified Risks

**Pancreatitis.** Acute pancreatitis has been reported in association with albiglutide and other GLP-1 receptor agonists in clinical trials and during postmarketing experience. Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether they are at increased risk for pancreatitis. Subjects with a history of pancreatitis or who are considered at significant risk of developing pancreatitis are excluded from entering the study. Subjects will be informed of the characteristic symptom of pancreatitis: persistent severe abdominal pain. If pancreatitis is suspected, investigational product should be promptly discontinued and if pancreatitis is confirmed, investigational product will not be restarted.

**Gastrointestinal events.** Albiglutide has not been studied in subjects with severe gastrointestinal (GI) disease, including severe gastroparesis. Subjects with severe gastroparesis will be excluded from the study. Use of albiglutide and other GLP-1 receptor agonists can be associated with GI side effects such as diarrhoea, nausea, and vomiting; the frequency of these events increased as renal function decreased. These types of GI reactions can be associated with dehydration and worsened renal function.

(see below and see Section 4.4.4). Other GI related adverse reactions with albiglutide include dyspepsia, gastro-oesophageal reflux disease and constipation.

**Hypoglycaemia.** Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycaemia. However, when used in combination with insulin (or insulin secretagogues) the risk of hypoglycaemia is increased. Investigators will be reminded that it may be necessary to reduce the dose of insulin or insulin secretagogues when starting study medication to reduce the risk of hypoglycaemia. Routine standard of care for subjects treated with insulin secretagogues and insulin includes advice about avoidance of hypoglycaemia which will be reinforced. All subjects are required to have a last indicator of glycemic control of above HbA1c = 7% which is expected to reduce the risk of hypoglycaemia when starting albiglutide.

**Immunogenicity.** Hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III programme. In the Phase III programme one subject (anti-albiglutide antibody negative) developed rash, itching and dyspnoea. Subjects with known allergy to any GLP-1 receptor agonist or excipients of albiglutide are excluded from the study. Subjects will be informed of the symptoms of severe hypersensitivity or allergy and be advised to seek medical assistance immediately. In the Phase III programme approximately 5% of subjects developed anti-albiglutide antibodies. Subjects who tested positive for anti-albiglutide antibodies experienced a similar glycaemic response (HbA1c and fasting plasma glucose) to those who did not test positive for antibodies. Other than injection site reactions (see below), the overall safety profile appeared similar among the subset of subjects who did and those who did not test positive for anti-albiglutide antibodies. Anti-albiglutide antibody formation is not expected to impact the overall safety of albiglutide treatment and therefore will not be measure routinely in this study.

**Injection site reactions.** Albiglutide injections may cause rash, erythema or itching and/or other reactions at the site of injection. Subjects will be advised that when injecting in the same region, to use a different injection site each week. In the Phase III program, most subjects with injection site reactions did not test positive for anti-albiglutide antibodies. However, injection site reactions were reported more frequently among those who did test positive for anti-albiglutide antibodies (41% of the antidrug antibody positive subjects reported one or more injection site reactions) than among those who were consistently antibody negative (14% of the antidrug antibody negative subjects reported one or more injection site reactions).

**Other adverse reactions** (e.g. pneumonia, atrial fibrillation/flutter, and appendicitis). In the Phase III programme in type 2 diabetes, other possible albiglutide related adverse reactions were identified. These events occurred at a cumulative incidence <3% in studies up to 3 years in duration. These events were reported more frequently with albiglutide than comparators.

#### 3.4.1.2. Potential Risks

**Thyroid C-cell tumours.** GLP-1 receptor agonists, including albiglutide increase serum calcitonin in rodents and other GLP-1 receptor agonists are associated with thyroid C-cell



focal hyperplasia and C-cell tumours in rodents. It is unknown whether GLP-1 receptor agonists are associated with thyroid C-cell tumours in humans, including medullary thyroid cancer (MTC). Subjects with a personal or family history of MTC or subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) are excluded from the study. Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. Routine monitoring of serum calcitonin is not recommended. However, if serum calcitonin is found to be elevated the subject should be referred to a specialist for further evaluation. If MTC or other thyroid C-cell neoplasia is diagnosed, investigational product will be discontinued.

**Other malignant neoplasms** Concerns have been raised regarding use of incretin based therapies and other malignancies such as pancreatic cancer [Egan, 2014], malignancy when used in combination with insulin based on hypotheses of biological plausibility [European Public Assessment Report, 2014], and haematological malignancies [FDA Summary Basis of Approval, 2014].

**Hepatotoxicity.** Hepatotoxicity is an area of interest in drug development. Patients with type 2 diabetes are at increased risk for liver enzyme abnormalities and disease related liver conditions. One subject treated with albiglutide in the Phase III clinical programme developed probable drug induced liver injury with an asymptomatic elevation in alanine amino transferase (ALT) and total bilirubin although the cases had some atypical features and complicating factors. Routine liver safety laboratory evaluations will be conducted and specific withdrawal criteria for elevated liver function tests have been defined (See Section 4.4.3).

**Subject population with severe renal impairment (eGFR <30 mL/min/1.73m<sup>2</sup>).** Experience in type 2 diabetes subjects with severe renal impairment is limited (in the Phase III programme a total of 19 subjects with eGFR <30 mL/min/1.73m<sup>2</sup> received albiglutide).

In a Phase 3 study of patients with varying degrees of renal impairment, in the albiglutide group, on-therapy GI AEs occurred with a higher incidence and higher event rate in subjects with moderate and severe renal impairment compared to those with mild renal impairment. Because these GI events may lead to dehydration and worsen renal function, worsening renal function will be closely evaluated as an AE of special interest, serum creatinine will be measured every 8 months, and subjects will discontinue IP if eGFR falls below 15 mL/min/1.73m<sup>2</sup>. Subjects with known severe renal impairment are excluded from the study (see Section 4.4.4).

**Drug Interactions.** Like other members of the class, albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the development programme, drug interactions studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant PK or PD effects. Investigators will be advised to take the effect of albiglutide on gastric emptying into account when prescribing concomitant medication.

**Pregnancy and Lactation.** Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. It is not known if albiglutide is secreted into

human milk during lactation. Given that albiglutide is an albumin-based protein therapeutic, it is likely to be present in human milk. Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation. Subjects who are breastfeeding, pregnant or planning a pregnancy during the course of the study are excluded. Additionally, all females of child-bearing potential must be taking adequate contraception during the study and have a negative pregnancy test prior to entry.

**Placebo control.** In subjects treated with placebo, symptoms and long-term risks of hyperglycaemia may not improve or may worsen. During the study, intensification of glucose-lowering treatments other than study drug will be allowed in both treatment arms with a treat-to-target approach. Albiglutide placebo injections may cause injection site reactions. Subjects will be advised when injecting into the same region to use a different injection site each week.

### **3.4.2. Benefit Assessment**

In subjects with type 2 diabetes albiglutide treatment resulted in clinically relevant lowering of HbA1c at both the 30 mg and 50 mg doses when given as monotherapy and in combination with metformin, sulfonylureas (SUs), thiazolidinedione or basal insulin. The durability of the effect on glycaemic control was shown over a study period of up to 3 years. Consistent with its mechanism of action, albiglutide was not associated with clinically relevant hypoglycaemia except when used in combination with an SU or insulin, and incidence rates with the combination were less than those reported with SUs or insulin alone. Treatment with albiglutide generally produced a steady reduction in weight over time.

For subjects not yet on insulin at the start of the study, data from the Phase III programme suggest that the use of albiglutide once weekly in a pen device may have the potential to delay the need to start daily insulin injections. This will be formally assessed within this trial. Similarly, it is possible that for those already taking basal insulin, albiglutide may delay the need to introduce short-acting prandial injections and for those taking basal/bolus or pre-mixed insulin, it may reduce the dosage of insulin and/or the number of daily injections needed to achieve good glycaemic control. These will also be evaluated in the study.

Subjects in the placebo arm will also be receiving effective anti-hyperglycaemic medication which will be titrated up or down as required to improve or maintain glycaemic control, and therefore these subjects should also demonstrate reductions in HbA1c, though weight gain (rather than weight loss) may occur depending upon the medication selected.

Finally, as a result of participating in a clinical trial, each subject will receive more contact with the study site than would be performed as part of their usual standard of care.



### **3.4.3. Overall Benefit:Risk Conclusion**

Taking into account the measures taken to minimise risk to subjects participating in this study, the known and potential risks identified with albiglutide are justified by the benefits have been demonstrated in subjects with type 2 diabetes.

## **4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA**

### **4.1. Inclusion Criteria**

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB for albiglutide and in the product label for those countries where marketing authorisation has been granted.

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

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

1. Men or women at least 40 years old with a diagnosis of type 2 diabetes.
2. Established cardiovascular disease, including at least 1 of the following:
  - a. Coronary artery disease with EITHER of the following:
    - Documented history of spontaneous myocardial infarction, at least 30 days prior to Screening.
    - Documented coronary artery disease (CAD)  $\geq$  50% stenosis in 1 or more major epicardial coronary arteries, determined by invasive angiography, or history of surgical or percutaneous (balloon and/or stent) coronary revascularization procedure (at least 30 days prior to Screening for percutaneous procedures and at least 5 years prior to Screening for coronary artery bypass graft (CABG)).
  - b. Cerebrovascular disease – ANY of the following:
    - Documented history of ischaemic stroke, at least 90 days prior to study entry.
    - Carotid arterial disease with  $\geq$  50% stenosis documented by carotid ultrasound, magnetic resonance imaging or angiography, with or without symptoms of neurologic deficit.
    - Carotid vascular procedure (e.g. stenting or surgical revascularisation), at least 30 days prior to Screening.
  - c. Peripheral arterial disease (PAD) with EITHER of the following:
    - intermittent claudication and ankle:brachial index  $< 0.9$  in at least one ankle

- prior non-traumatic amputation, or peripheral vascular procedure (e.g. stenting or surgical revascularisation), due to peripheral arterial ischaemia.
3. HbA1c >7.0% (53 mmol/mol) based on the most recent documented laboratory assessment measured no more than 6 months prior to randomization. Local laboratory HbA1c values taken as part of usual care are permitted.
  4. Female: subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test for females of reproductive potential only), not breastfeeding, and at least one of the following conditions applies:
    - a. Reproductive potential and agrees to follow one of the options listed in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (e.g. combined oral contraceptive pill; see [Appendix 2](#)) from 30 days prior to the first dose of study medication and until after the last dose of study medication and completion of the follow-up visit.

This does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent. Other situations in which contraception in FRP may not need to be mandated should be discussed with the Medical Monitor.
    - b. Non-reproductive potential defined as either:
      - Pre-menopausal with one of the following: (i) documented tubal ligation; (ii) documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion; (iii) hysterectomy; or (iv) documented bilateral oophorectomy, or;
      - Postmenopausal defined as 12 months of spontaneous amenorrhea and age appropriate (i.e. >50 years). In questionable cases, a blood sample with simultaneous follicle stimulating hormone (FSH) >40 mIU/mL and oestradiol <40 pg/mL (<140 pmol/L) is confirmatory, depending on local laboratory ranges. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.
  5. Able and willing to provide informed consent.

## 4.2. Exclusion Criteria

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

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

1. eGFR calculated using MDRD formula  $<30\text{mL}/\text{min}/1.73\text{m}^2$  (based on the most recent documented serum creatinine laboratory assessment measured no more than 6 months prior to randomization. Local laboratory creatinine values taken as part of usual care are permitted) or renal replacement therapy.
2. Use of a GLP-1 receptor agonist at Screening.
3. Severe gastroparesis requiring therapy within 6 months prior to Screening.
4. History of pancreatitis or considered clinically at significant risk of developing pancreatitis during the course of the study (e.g. due to symptomatic gallstones, excess alcohol use).
5. Personal or family history of medullary carcinoma of the thyroid or subject with MEN-2. Personal history of pancreatic neuroendocrine tumours. In the opinion of the investigator, the subject has a medical history which might affect his / her ability to remain in the study for its entire duration, or which might limit management, such as life expectancy of  $<5$  years (e.g. due to active malignancy).
6. Subject has a medical history which in the opinion of the investigator might limit the individual's ability to take trial treatments for the duration of the study or to otherwise complete the study.
7. Breastfeeding, pregnancy, or planning a pregnancy during the course of the study. Pregnancy test will be required in women of child bearing potential. Women who have undergone a sterilisation procedure or who are clearly post-menopausal will not be required to undergo pregnancy testing. Women who have developed spontaneous secondary amenorrhoea of 12 months or more where post-menopausal status is in doubt, a blood sample where FSH  $>40\text{MU}/\text{ml}$  and oestradiol  $<40\text{ pg}/\text{mL}$  ( $<140\text{ pmol}/\text{L}$ ) are simultaneously measured will be considered confirmatory.
8. Known allergy to any GLP-1 receptor agonist or excipients of albiglutide.
9. Use of another investigational product within 30 days or according to local regulations, or currently enrolled in a study of an investigational device.
10. Any other reason the investigator deems the subject to be unsuitable for the study.

### **4.3. Screening/Baseline Failures**

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements [Schulz, 2010], and respond to queries from regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any SAEs.

Re-screening of subjects who did not meet the eligibility criteria for HbA1c or creatinine based on local laboratory values taken as part of usual care is permitted. If values were based on laboratory results as part of usual care then one re-test is permitted within the protocol at Screening. Any future re-screening will be based on laboratory results obtained as part of usual care.

#### **4.4. Criteria for Early Discontinuation of Investigational Product**

The primary analysis will be conducted on an ITT analysis basis so it is important that every subject is followed for the duration of the study, regardless of whether the subject continues to take investigational product, unless consent for all follow up is actively withdrawn.

The requirements for handling early discontinuations from investigational product are described below. Details of the requirements for subject follow-up are provided in Section 4.5.

##### **4.4.1. Early Discontinuation of Investigational Product**

If a subject chooses to discontinue investigational product between scheduled face-to-face visits they should be encouraged to contact the investigator site by telephone. Subjects should first be counselled to consider temporary discontinuation of investigational product prior to choosing to discontinue investigational product permanently, unless the reason for discontinuation is one of those listed below (Reasons for Discontinuation of Investigational Product). If the discontinuation is permanent, the subject should be asked to attend the clinic as soon as possible to complete the assessments as for the final study visit (see Table 1) and then continue in the study for follow-up. The procedures for follow-up for a subject who permanently discontinues treatment with investigational product prior to the study end are given in Section 4.5.

In all cases, reasons for discontinuation of investigational product and the date of last dose will be recorded.

##### **4.4.2. Reasons for Discontinuation of Investigational Product**

Any subject experiencing the following will be required to discontinue investigational product:

- AE:
  - Pancreatitis, acute or chronic.
  - Pancreatic cancer.
  - MTC or other thyroid C-cell neoplasia. In subjects where a treatment emergent thyroid nodule is identified, if serum calcitonin is measured at the discretion of the Investigator (e.g., per local guidelines) and found to be >100 ng/L this should prompt further investigation for MTC and potential interruption or discontinuation of investigational product until diagnosis has been resolved.

- Liver chemistry abnormalities exceeding the threshold criteria outlined in Section 4.4.3
- Severe allergic/hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology.
- Other AE which, in the opinion of the investigator precludes continuation of dosing.
- eGFR<15ml/min/1.73m<sup>2</sup> (Section 4.4.4) or the need for renal replacement therapy.
- Subject becomes pregnant during the study.
- Need for chronic use of a prohibited concomitant medication (Section 5.6.2)
- Decision by subject or proxy.
- Sponsor terminated study.
- Investigator site closed and subject was unable to transfer to another investigative site.

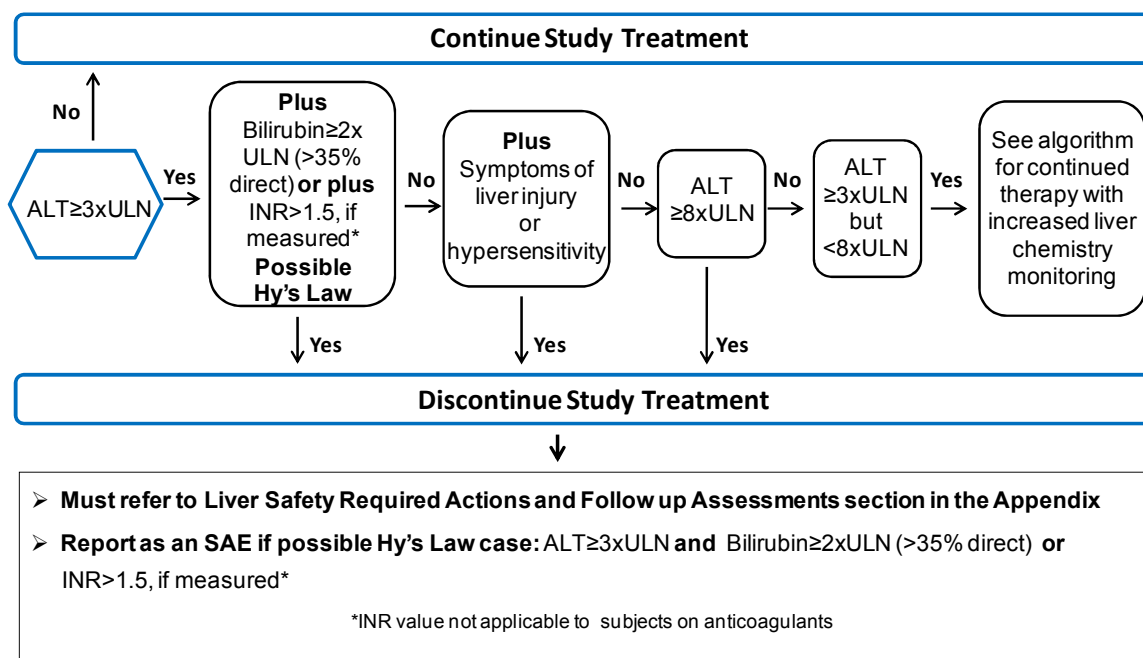
If investigational product is discontinued, the subject should continue in the study and be followed until the final study visit as detailed in Section 4.5.

#### 4.4.3. Liver Chemistry Stopping Criteria

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

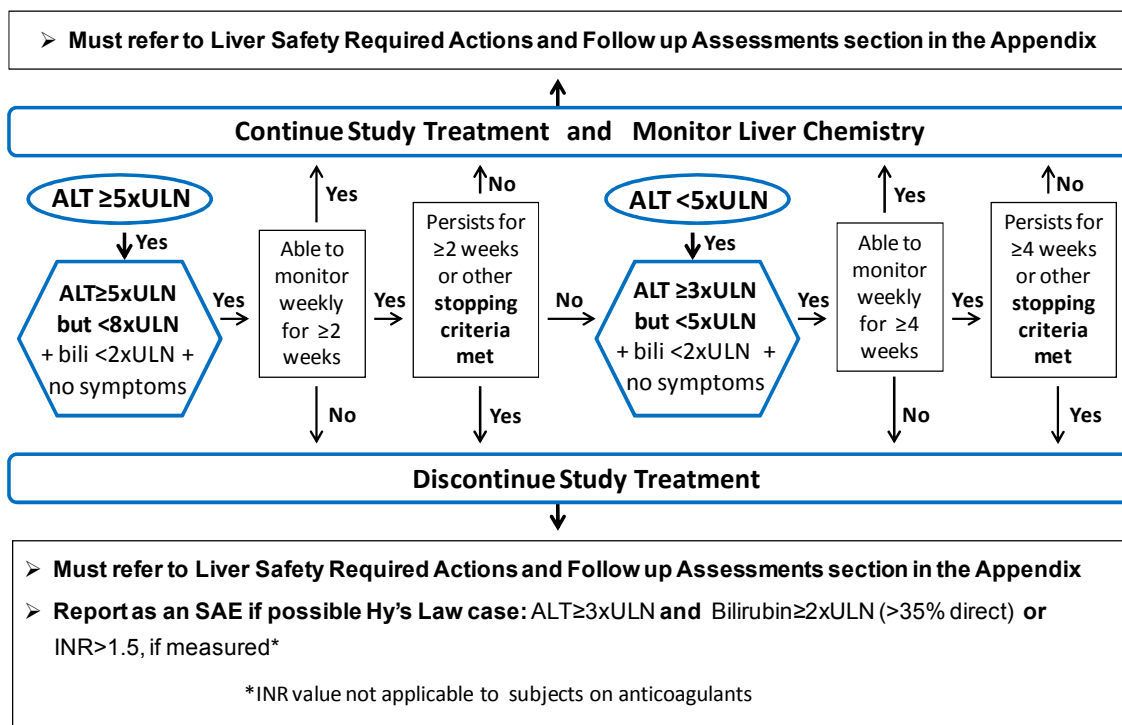
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

#### Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver safety required actions and follow up assessments section can be found in [Appendix 3](#).

### Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3 \times \text{ULN}$ but $< 8 \times \text{ULN}$



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 3](#).

Drug re-challenge following drug induced liver injury is not allowed.

Restart may be considered if GSK Medical Governance approval is granted (see [Appendix 4](#) for details). Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with human leukocyte antigen (HLA) markers of liver injury.

#### 4.4.4. eGFR Stopping Criteria

A baseline eGFR  $\geq 30 \text{ mL/min/1.73m}^2$  is a requirement for entering the study. Subjects can continue to take investigational product if functioning well as long as eGFR is  $\geq 15 \text{ mL/min/1.73m}^2$ .

During this study, if a subject's eGFR approaches  $30 \text{ mL/min/1.73m}^2$  closer monitoring of renal function is considered prudent, according to standard clinical practice. Particular

care should be taken to monitor renal function in subjects with renal impairment reporting severe adverse GI events. If eGFR is  $<15\text{mL}/\text{min}/1.73\text{m}^2$  and considered irreversible based on consecutive measurements the investigational product should be discontinued, the subject continue in the study and be followed until the final study visit.

If eGFR is  $<15\text{mL}/\text{min}/1.73\text{m}^2$  and the patient is considered to have temporary acute kidney injury that is potentially reversible, the investigational product should be temporarily discontinued until the eGFR is stable and  $\geq 15\text{mL}/\text{min}/1.73\text{m}^2$ . Events considered to reflect worsening renal function should be reported as SAE/AEs and targeted eCRFs completed for this AE of special interest (Section 6.2.3).

#### **4.5. Procedures for Subject Follow-up**

As described in Section 4.4, subjects who permanently discontinue investigational product will be asked to attend the clinic as soon as possible. They will continue in the study for follow-up. Five weeks ( $\pm 1$  week) after discontinuation of investigational product, subjects will be contacted for a follow-up by telephone. They will be asked to return to clinic according to the 8 monthly visit schedule and in addition be contacted by telephone at a time corresponding to the 4-monthly visit they would have otherwise made to replenish study medication supply. If instead of these interim telephone contacts the subject prefers to attend clinic every 4 months as originally scheduled that is an acceptable alternative.

If a subject permanently discontinues investigational product and is unable to attend visits in-person, he/she will be contacted by telephone or other methods to assess study outcomes and vital status, unless the subject has specifically withdrawn consent for all forms of contact. Follow-up of subjects who withdraw consent for contact is described below.

Every effort should be made to educate the subjects on the importance of remaining in the study and attending scheduled study visits including those required after early discontinuation of investigational product.

Other subject follow-up options to collect study outcomes and vital status should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes and vital status is acceptable to the subject, then the subject will be deemed not to have withdrawn consent for follow-up.

##### **4.5.1. Withdrawal of Consent for Contact**

Subjects who no longer wish to attend study visits in-person will be asked to be contacted by telephone or other methods to assess study outcomes and vital status. However, if a subject specifically withdraws consent to be contacted for additional information, no further study visits or study-related telephone contacts can be conducted. Information regarding study outcomes or vital status will continue to be collected from available sources including those in the public domain. Additionally, alternative permitted options to obtain study outcomes and vital status will be reviewed based on accepted local laws and regulations. For any subject who withdraws consent for contact, the study site will be

asked to document the discussion with the subject regarding each of the contact options that were offered.

#### **4.5.2. Subjects Deemed Lost to Follow-up**

Finally, investigators should make every effort to contact subjects who are deemed lost to follow-up and who have not withdrawn consent to follow-up contacts, including pursuing any alternative contact methods permitted by local regulations. Where permitted, a third party may be used to locate alternative subject contact information that will be provided to the investigator. All attempts to contact subjects will be documented in the subject's eCRF and source notes.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject. Should the subject continue to be unreachable, then and only then will he/she be considered "Lost to Follow-up". Nonetheless, efforts to attempt to locate and contact the subject will continue until the study end.

## **5. STUDY TREATMENTS**

### **5.1. Investigational Product and Other Study Treatment**

Albiglutide (and albiglutide matching placebo) will be provided as a fixed-dose, fully disposable pen injector system for delivery of the investigational product (albiglutide or albiglutide matching placebo) from a prefilled dual chamber glass cartridge that is an integral part of the pen. The pen is intended for single use by the subject. It is designed for manual reconstitution of the dose, priming and insertion of the pen needle, and manual injection by the subject.

Albiglutide (or albiglutide matching placebo) is intended for self-administration as a subcutaneous injection in the abdomen, thigh or upper arm region. Rotation of use of injection sites is recommended. Albiglutide and insulin may be injected in the same body region but the injections should not be adjacent to each other. The albiglutide pen includes a mechanical locking system that prevents the user from manipulating the dose button before the cartridge has been fully reconstituted. Reconstitution is performed through rotation of the pen housing parts. The pen is designed to work with standard pen needles.

When the injector pen product is reconstituted by the subject, a neutral, isotonic solution is produced. Separate pens are required to deliver either 30 mg of albiglutide, 50 mg of albiglutide, or matching placebo in a 0.5-mL injection volume.

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



Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

The investigational product (albiglutide and albiglutide matching placebo) must be stored in a secure area at 2°C to 8°C and protected from freezing. Each site must maintain a temperature log. Access to and administration of the investigational product will be limited to the investigator and authorised site staff (investigator or designee). Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Procedures for the disposal of unused study treatment will be provided in the SRM.

Investigational product (albiglutide or albiglutide matching placebo) will be administered once weekly by subcutaneous injection. The first dose is to be administered at the clinic. The starting dose of albiglutide will be 30 mg once weekly. If at any stage after 5 weeks of treatment in the opinion of the investigator the subject needs to have intensified therapy to improve glycaemic control, the dose of investigational product should be increased before altering the doses of other glucose-lowering medication. In this case the subject will be called in for an unscheduled visit to supervise an increase in dose from 30 mg to 50 mg. Subjects randomly assigned to albiglutide matching placebo will also go through the increased dose procedure to maintain study blind. If a subject experiences tolerability issues with the higher, 50mg dose then the investigator may decrease the dose back to 30 mg without the need for an unscheduled visit to supervise down titration, other than for the subject to collect pens of the correct dose.

Albiglutide (or albiglutide matching placebo) may be administered at any time of day without regard to meals. Preferably, it should be administered once a week on the same day each week. The day of weekly administration can be changed if necessary as long as the last dose was administered 4 or more days previously. If a dose is missed, it should be administered as soon as possible within 3 days after the missed dose. Thereafter, subjects can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, subjects should wait and administer their next regularly scheduled weekly dose.

If a subject misses 4 or more consecutive doses, the investigator should contact the medical monitor to discuss options for helping assure better compliance.

## **5.2. Treatment Assignment**

Subjects will be assigned to study treatment in accordance with the randomisation schedule.

Randomised treatment assignment will be done via the Interactive Voice Response System (IVRS), and randomisation will be implemented based on a sequestered fixed randomisation schedule. Study centre personnel will call the IVRS once a subject has met all prerequisites for randomization; the IVRS will assign treatment.

Blinded study centre personnel will receive a randomisation notification indicating only the unique subject identifier and the date and time of randomisation. Each subject number will be a unique identifier. Once a subject number has been assigned, the number will not be reused even if the subject withdraws before receiving any investigational product. Details of the treatment assignment process are contained in the SRM.

### 5.3. Blinding

This is a double-blind study, neither the subject nor the study physician will know which of the two treatments (albiglutide or placebo) the subject is receiving.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency or in the event of a serious medical condition, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator**. Investigators have direct access to the subject's individual study treatment. It is preferred (but not mandatory) that the investigator first contacts the GSK Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment. If GSK study personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be fully documented in the appropriate data collection tool.

If a subject is unblinded by the investigator or treating physician then discontinuation of investigational product treatment for that subject will be at the discretion of the investigator. However, the subject should continue to be followed in the study (see Section 4.5).

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

### 5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned unused by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

## **5.5. Treatment Compliance**

Subjects will be instructed to return all unused and used injector pens at the visits specified in the Time and Events Table ([Table 1](#)) in order to perform drug accountability and determine compliance. Subjects will be provided with a sharps container for the disposal of used pens. To comply with health and safety considerations there will be no count made of used pens; only returned unused pens will be counted. In addition, subjects will be provided with a pre-printed card at each dispensing visit to record the date of each dose. The card is to be returned at the next dispensing visit with the unused pens.

## **5.6. Concomitant Medications and Non-Drug Therapies**

### **5.6.1. Permitted Medications and Non-Drug Therapies**

The usual care provider will manage the subjects according to standard of care, following local prescribing information. Close adherence to professional society guidelines for standard of care therapies in type 2 diabetes and cardiovascular disease will be emphasized during study conduct. Standard of care is described in greater detail in [Section 3.2](#).

Unless specified as a prohibited medication in [Section 5.6.2](#), all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned.

Like other members of the class, albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. This should be taken into account by investigators when prescribing concomitant medication.

It may be necessary to reduce the dose of concomitantly administered insulin secretagogues (such as SUs) or insulin to reduce the risk of hypoglycaemia when starting albiglutide.

All concomitant anti-hyperglycaemic medications (name of agent, total daily dose, start and stop dates) will be recorded in the eCRF at each visit. Concomitant cardiovascular medications taken during the study will also be recorded at each visit by class of agent. Additionally, all medications used within the 30 days prior to the onset and throughout the duration of an SAE, AE of special interest ([Section 6.2.3](#)), or an AE leading to discontinuation of investigational product will be recorded as individual agents, reason for use, together with start dates (and stop dates if applicable) and any changes since any previous AE.

### **5.6.2. Prohibited Medications and Non-Drug Therapies**

Subjects may not take a GLP-1 receptor agonist (other than blinded investigational product), nor any investigational drug, during the study (and any follow-up period after discontinuing investigational product).

If a subject receives a prohibited medication, a protocol deviation will be recorded.

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

Following the final study visit subjects will be contacted by telephone  $5 \pm 1$  weeks after last dose of study medication to assess any AEs ongoing since the last visit or newly emergent.

Subjects will be treated as deemed appropriate by the investigator following the end of the study. Investigational product will not be provided to subjects by GSK after the end of the study.

The half-life of albiglutide is approximately 5 days, and significant therapeutic concentrations can persist for 3 to 4 weeks after discontinuation. The choice of other medicinal products and dose selection should be considered accordingly, as adverse reactions may continue and efficacy may, at least partly, persist until albiglutide levels decline.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition whether or not GSK is providing specific post study treatment.

### **5.8. Treatment of Study Treatment Overdose**

No data are available with regard to albiglutide overdose in humans. The highest recommended dose of albiglutide is 50 mg once weekly.

During clinical studies of subjects with type 2 diabetes, the highest dose of albiglutide administered was 100 mg subcutaneously every four weeks for 12 weeks. This dose was associated with an increased frequency of nausea, vomiting, and headache.

There is no specific antidote for overdose with albiglutide. In the event of a suspected overdose, the appropriate supportive clinical care should be instituted, as dictated by the subject's clinical status. Anticipated symptoms of an overdose may be severe nausea, vomiting or headache. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the half-life of albiglutide (5 days).

## **6. STUDY ASSESSMENTS AND PROCEDURES**

The schedule of study assessments is shown in [Table 1](#). Detailed procedures for each assessment are provided in the SRM.

**Table 1 Time and Events Table**

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post rand.)	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	Follow up Phone Call 5 ± 1 weeks after last IP dose
Written informed consent	X							
Review of Inc/excl criteria	X	X						
Demography & directed medical history	X							
Assessment of MACE and micro-vascular events				X		X	X	
HbA1c	X <sup>5</sup>			X		X	X	
Serum creatinine (eGFR)	X <sup>5</sup>					X	X	
Liver Function Tests <sup>6</sup>		X				X	X	
Genetic sampling <sup>7</sup>		X						
Patient reported outcomes questionnaires <sup>8</sup>		X				X	X	
Key concomitant non-diabetes medication		X		X		X	X	X
Diabetes medication		X		X		X	X	X
Study drug reminder			X	X	X	X		
Physical examination <sup>9</sup>		X				X	X	
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X	X	X	X	X
Pregnancy test <sup>10</sup>	X	X						
Study drug dispense/compliance <sup>11</sup>		X		X	X	X	X	

- Subjects who discontinue investigational product should be handled as described in Section 4.4 and Section 4.5.
- Assessments per the Month 4 visit will alternate with those per the Month 8 visit throughout the study i.e., assessments at months 4, 12, 20 etc will be per Month 4; those at month 8, 16, 24 etc..will be per Month 8.
- Screening and Randomisation can occur at the same visit if all eligibility information is available. If Screening and Randomisation occur at the same visit assessments should not be duplicated.
- Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.
- HbA1c and creatinine assessed using local laboratories at Screening visit and measured no more than 6 months prior to randomisation. If HbA1c or creatinine have not been assessed in the previous 6 months assessments to be performed via a central laboratory and results available prior to randomization. The investigator has the discretion to repeat screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.
- Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT. Blood samples for LFTs at randomization must be collected prior to the first dose of investigational product.
- Informed consent for genetic research must be obtained before collecting a sample. Genetics sample can be collected at any time after genetic consent has been obtained and the subject has been randomised.
- TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
- See Section 6.2.7.
- Only applies to women of child bearing potential. At screening perform urine pregnancy test. If positive, send serum sample to the central laboratory for confirmation. At Randomisation perform a urine pregnancy test. If result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised. If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. See Section 6.2.6.
- Study drug dispensing not performed at final visit, compliance check not performed at Randomisation.

## 6.1. Critical Baseline Assessments

Disease, and therapy history, including cardiovascular medical history/risk factors will be assessed at Baseline. Investigators are encouraged to implement lifestyle modifications and adjust or initiate the appropriate pharmacotherapy throughout the study as recommended by current locally followed therapeutic cardiovascular and diabetes guidelines for participants in the study. Screening and randomisation can occur at the same visit depending on availability of information to determine eligibility of the subject to enter the study.

## 6.2. Safety

The following sections provide further detail on the safety assessments. Planned time points for all safety assessments are listed in the Time and Events Table ([Table 1](#)). Unscheduled visits will occur as medically necessary. Detailed procedures for obtaining each assessment are provided in the SRM.

Safety endpoints are described in [Section 2](#) and will include monitoring of cardiovascular events ([Section 6.2.1](#)), deaths, AEs of special interest ([Section 6.2.3](#)), clinically significant microvascular events ([Section 6.2.4](#)), SAEs and AEs leading to discontinuation of investigational product.

Liver chemistry stopping and follow-up criteria and AEs are described in [Section 4.4.3](#) and [Appendix 3](#).

### 6.2.1. Cardiovascular Events

Events referred to the CEC by the investigator as potential endpoints or transient ischemic attacks (TIAs) will not be collected or reported as SAEs, regardless of the adjudication outcome ([Section 6.2.2](#)). These events will be reviewed by an Independent Data Monitoring Committee ([Section 9.8](#)).

The CEC will review and adjudicate the following clinical events:

- Myocardial infarction
- Stroke
- Unstable angina requiring hospitalization
- Hospitalization for heart failure
- Sudden cardiac death
- TIA
- In addition, all clinical events submitted for adjudication and all other SAEs with a fatal outcome will be reviewed and adjudicated to classify the cause of death as cardiovascular or non-cardiovascular.

When the local investigator reported event and the CEC decision on the nature of the event differ, the CEC's decision will be considered final. The detailed descriptions of the endpoint (and TIA) definitions necessary for adjudication are contained within the CEC Charter (available on request). The guiding principle will be the "2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular and Stroke End Point Events for Clinical Trials" [ACC/AHA, 2014] and the "Third Universal Definition of Myocardial Infarction" endorsed by the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation (WHF) [Thygesen, 2012].

Source documentation required to support the adjudication of the events is described in the SRM. Recording of potential endpoint and TIA events in the eCRF and submission of source documentation will be required for clinical events meeting reporting criteria whether or not an endpoint event is suspected by the investigator.

#### **6.2.1.1. Other CV Events**

GSK has identified other CV events of special interest for all clinical studies. Investigators will be required to fill out event specific data collection tools for the following cardiovascular events which meet SAEs criteria or are non-serious events that result in discontinuation of investigational product:

- Arrhythmias (other than atrial fibrillation/flutter, see Section 6.2.3)
- Valvulopathy
- Pulmonary hypertension
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation (other than urgent revascularisation for unstable angina, a component of a secondary endpoint)

This information should be recorded in the specific cardiovascular eCRF within one week.

#### **6.2.2. Adverse Events (AE) and Serious Adverse Events (SAEs)**

The definitions of an AE or SAE can be found in [Appendix 5](#).

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

For this study events of myocardial infarction, stroke, unstable angina requiring urgent revascularization, hospitalization for heart failure, TIA and sudden cardiac death will not be collected or reported as AEs or SAEs. These events will be collected separately, subjected to blinded adjudication by an independent CEC using prespecified diagnostic criteria, and reported separately (Section 6.2.1.1). All other events that meet serious criteria as defined in [Appendix 5](#) should be reported as SAEs.

All events with an outcome of death will be adjudicated to classify the cause of death as specifically cardiovascular or non-cardiovascular. Any event resulting in death should be reported as a SAE unless the event is myocardial infarction, stroke, unstable angina w/ urgent revascularization, Heart failure, TIA or sudden cardiac death which the protocol specifies are not to be collected as adverse events.

The study will not collect all non-serious AEs. Non-serious AEs leading to discontinuation of investigational product and non-serious AEs of special interest (see Section 6.2.3) will be collected.

Any events not specifically addressed above should be reported as an AE or SAE according to the definitions in [Appendix 5](#).

#### **6.2.2.1. Time period and Frequency for collecting AE and SAE information**

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 6.2.2.3), at the timepoints specified in the Time and Events Table ([Table 1](#)).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in [Appendix 5](#).
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in [Appendix 5](#).

#### **6.2.2.2. Method of Detecting AEs and SAEs**

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

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”



- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

Additionally subjects will be asked specific questions about the occurrence of AEs of special interest (Section 6.2.3).

#### **6.2.2.3. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 6.2.3) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 4.5). Further information on follow-up procedures is given in [Appendix 5](#).

#### **6.2.2.4. Sentinel Events**

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/severe neutropenia
- Anaphylaxis and anaphylactoid reactions (see also Section 6.2.3)
- Hepatotoxicity (see also Section 6.2.3)
- Acute renal failure
- Seizure
- Stevens Johnson syndrome/toxic epidermal necrosis

#### **6.2.2.5. Regulatory Reporting Requirements for SAEs**

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

### **6.2.3. Adverse Events of Special Interest**

The investigator or site staff will be responsible for detecting, documenting and reporting events the following AEs of special interest:

- Development of thyroid cancer
- Haematologic malignancy
- Pancreatic cancer
- Pancreatitis
- Injection site reactions
- Immunological reactions (e.g., drug hypersensitivity reactions involving anaphylaxis/anaphylactoid reactions, acute bronchoconstriction, angioedema, and/or acute urticaria)
- Severe hypoglycaemia events (which includes all events meeting the definition of SAEs [Appendix 5](#))
- Hepatic events
- Hepatic enzyme elevations (including GGT)
- Serious GI events
- Appendicitis
- Atrial fibrillation/flutter
- Pneumonia
- Worsening renal function
- Diabetic retinopathy

The results of any investigation should be recorded in the relevant sections of the subjects' eCRFs. In addition, for thyroid, pancreas or haematological malignancies a copy of the histopathology report and a discharge summary if the subject was admitted, or any available case summary (e.g. clinic letter), is to be provided to the Sponsor, if available.

Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. In subjects where a treatment emergent thyroid nodule is identified, if serum calcitonin is measured at the discretion of the Investigator (e.g., per local guidelines) and found to be >100 ng/L this should prompt

further investigation for MTC and potential interruption or discontinuation of investigational product until diagnosis has been resolved. If MTC or other thyroid C-cell neoplasia is diagnosed, albiglutide will be discontinued.

A Pancreatitis Adjudication Committee composed of independent specialists in gastroenterology will review all cases of possible pancreatitis.

Subjects should also be closely monitored for signs of potential allergic or drug hypersensitivity reactions including anaphylaxis, angioedema, generalized urticaria, and other potential manifestations of systemic allergic or drug hypersensitivity reactions. A serum sample should be taken as soon as possible after any such event in order to measure antibody to the drug. Instructions for sample processing are in the SRM. These events should be reported as AEs or SAEs based on the clinical evaluation of the subject. The reactions should be followed to completion as typical for any AE or SAE. Subjects with allergic or drug hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology should have investigational product withdrawn and not re-introduced.

Episodes of severe hypoglycaemia will be recorded according to subject report. Severe hypoglycaemic incidents will be defined as those episodes of hypoglycaemic symptoms for which the subject required assistance from another person and from which the subject recovered promptly after oral carbohydrate, intravenous glucose, glucagon administration or other resuscitative actions (definition per ADA Workgroup on Hypoglycaemia [Sequist, 2013]). Additionally, all episodes of hypoglycaemic symptoms which in the investigator's opinion meet the definition of a SAE (defined in [Appendix 5](#)) will be included as severe hypoglycaemic episodes. During this study, if a subject's eGFR approaches 30mL/min/1.73m<sup>2</sup> closer monitoring of renal function is considered prudent, according to standard clinical practice. If eGFR is <15mL/min/1.73m<sup>2</sup> follow the procedure set out in Section [4.4.4](#).

#### **6.2.4. Clinically Important Microvascular Events**

Clinically important microvascular events are defined as the following: need for renal transplant or dialysis, new diabetes-related blindness, and procedures (laser photocoagulation or anti-vascular endothelial growth factor treatment or vitrectomy for diabetic retinopathy/eye disease). Clinically important microvascular events will be reported as recorded in the eCRF by the investigator without adjudication.

The AEs associated with the above outcomes or treatments should be reported separately as an AE or SAE according to the definitions in [Appendix 5](#).

#### **6.2.5. Pregnancy**

- If a subject becomes pregnant during the study they should discontinue Investigational Product.
- Details of all pregnancies in female subjects will be collected after the start of dosing and until the end of the Post-treatment Follow-up Period.

- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in [Appendix 6](#).

#### **6.2.6. Clinical Laboratory Assessments**

All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule ([Table 1](#)). Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all central laboratory safety parameters will be provided to the site.

If additional non-protocol specified laboratory assessments result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE of special interest or dose modification) the results must be recorded in the CRF.

Refer to the SRM/laboratory manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

The following laboratory assessments will be performed: serum creatinine, HbA1c, liver function tests [AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin, GGT], and urine and serum  $\beta$ hCG pregnancy test (for women of child bearing potential). All study-required laboratory assessments will be performed by a central laboratory, with the exception of HbA1c and creatinine at Screening and urine pregnancy test at Screening/Randomization.

#### **Screening HbA1c and serum creatinine**

Screening HbA1c and serum creatinine values should be based on the most recent local laboratory values taken as part of usual care within the previous 6 months and the values entered into the eCRF. These assessments must have been performed at an accredited laboratory. HbA1c screening results must be either Diabetes Control and Complications Trial (DCCT) aligned or International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardized. HbA1c screening results from point of care equipment are acceptable provided that the equipment is maintained by an accredited laboratory. If HbA1c or creatinine have not been assessed in the previous 6 months, laboratory assessments will be performed via the central laboratory to determine eligibility (if a local laboratory is used in error the results are acceptable for determining eligibility). The investigator has the discretion to repeat screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.

Re-screening of subjects who did not meet the eligibility criteria for HbA1c or creatinine based on local laboratory values taken as part of usual care is permitted. If values were based on laboratory results as part of usual care then one re-test is permitted within the protocol at Screening. Any future re-screening will be based on laboratory results obtained as part of usual care.

**Pregnancy testing (for women of childbearing potential)**

At the screening visit perform a urine pregnancy test. If the urine pregnancy test is positive, send a serum blood sample to the central laboratory for confirmation of pregnancy.

At the Randomisation visit perform a urine pregnancy test. If the result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised (provided all other eligibility criteria have been met).

If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. Do not randomise if the urine pregnancy test is positive; send a serum blood sample to the central laboratory for confirmation of pregnancy. If the urine pregnancy test is negative then the subject can be randomised at the same visit (provided all other eligibility criteria have been met).

**6.2.6.1. Estimated Glomerular Filtration Rate (eGFR)**

Serum creatinine will be measured every 8 months by a central laboratory. It will be used to calculate eGFR using the MDRD formula [Levey, 2009], namely:

$$\text{eGFR (ml/min/1.73m}^2\text{)} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}).$$

**6.2.7. Physical examination**

A general physical examination, including height and neck (thyroid), will be performed at randomization. A targeted physical examination will be performed at all other time points as specified in the Time and Events Table (Table 1). The targeted physical examination will evaluate the cardiovascular system and injection sites and will include measurement of blood pressure and heart rate taken with the subject either in a semi-recumbent or seated position after at least a 5-minute rest period.

**6.3. Value Evidence and Outcomes****6.3.1. Value Evidence and Outcomes Assessments****6.3.1.1. Treatment Related Impact Measure – Diabetes (TRIM-D)**

In order to evaluate satisfaction with treatment and to compare satisfaction across treatment groups, the TRIM-D questionnaire will be self administered by all subjects at baseline and at each 8 month visit (and, to the extent possible, at the time of study completion or withdrawal from the study).

The TRIM-D, developed in 2009, is a 28-item treatment satisfaction measure scored to produce 5 sub-scale scores (Treatment Burden, Daily Life, Diabetes Management,

Psychological Health, and Compliance) as well as a total score. It is available in a wide range of translations.

The TRIM-D development, in accordance with the principles of the Food and Drug Administration Patient Reported Outcome Guidance document, was based on findings from the published literature including content from already-existing treatment satisfaction measures as well as significant input from subjects with type 1 and with type 2 diabetes and from expert diabetes clinicians. The TRIM-D has been evaluated in a sample of 507 subjects (74% with type 2 diabetes) and has been shown to have acceptable reliability and validity [Brod, 2009a]. Its responsiveness was also evaluated in a sample of 242 subjects (71% with type 2 diabetes) and found to be acceptable [Brod, 2009b]. Some preliminary work has been done on estimating its minimal important difference but this needs further exploration [Brod, 2009b].

#### **6.3.1.2. EQ-5D**

The EQ-5D will be self-administered by subjects in order to measure generic health status. Combining the EQ-5D with the disease-specific TRIM-D, which is designed to have maximum sensitivity to relevant aspects of disease related treatment, will provide a more robust evaluation of the impact of treatments for type 2 diabetes and allow for clearer interpretation of study results. TRIM-D results, if consistent with the general trends seen in the EQ-5D, will have enhanced credibility.

The EQ-5D is a standardized instrument used to evaluate generic health-related quality of life. It is applicable to a wide range of health conditions and treatments, and it provides a simple descriptive profile and a single index value for health status. It is also used to provide utilities, or preference weights, for use in economic (cost effectiveness) evaluations. It is available in 141 self complete official language versions.

The EQ-5D has been used extensively in studies to measure the impact of type 2 diabetes and treatments for the disease. A systematic review identified 54 publications reporting EQ-5D responses and 39 papers presenting evidence on the measurement properties of the EQ-5D in this population [Janssen, 2011]. This evidence supported the validity, reliability, and responsiveness of the EQ-5D for evaluating health-related quality of life in subjects with type 2 diabetes. Other studies reported that index scores from the EQ-5D have been shown to be an independent predictor of the risk of mortality, future vascular events, and other complications in people with type 2 diabetes [Clarke, 2009]. In addition, the SHIELD longitudinal study (1,741 respondents with type 2 diabetes and 4,543 without diabetes) used the EQ-5D to assess the 5-year changes in health-related quality of life in type 2 diabetes [Grandy, 2012].

#### **6.3.1.3. Exploratory Diabetes Management Questions**

In addition to the standardised instruments described above, patient experience in relation to the management of their diabetes will be evaluated in a subset of sites using a small number of self-administered diabetes management questions. These types of customized questions have been used successfully in asthma and in diabetes when patients are involved with goal-setting [Juniper, 1992; Anderson, 2010]. This tailored approach is an

opportunity to capture data in the study that are not otherwise available from standard PRO measures such as the TRIM-D and the EQ-5D. As an exploratory endpoint, this set of questions (3 items at baseline, and at each 8 month follow-up visit) imposes very little patient or site burden, but can offer critical insight into the one area of the patient's choosing that s/he finds most difficult to manage. In addition, this patient-centred endpoint has the potential to be sensitive to changes over time.

These questions have been developed by GSK based on factors identified as important to subjects in the development of published, validated and reliable subject reported outcomes instruments in type 2 diabetes.

#### **6.3.1.4. Healthcare Resource Utilisation**

Data will be collected on the following healthcare resource use:

- All cause hospitalisations and related healthcare resource use.

Healthcare resource use data will be collected in order to facilitate subsequent health-economic analyses comparing costs between albiglutide added to standard of care and placebo added to standard of care (cost is not an end point in the study).

Data on all-cause hospitalizations and related inpatient healthcare resource use will be collected. This will include:

- All-Cause hospitalisation including: Admission and discharge diagnoses (primary and secondary), length of stay, level/type of ward, and time spent in Intensive Therapy Unit (or equivalent).

#### **6.4. Genetic Research**

Information regarding genetic research is included in [Appendix 1](#).

### **7. DATA MANAGEMENT**

- For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

## **8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS**

### **8.1. Hypotheses**

This trial will examine the following primary question:

- Whether albiglutide is non inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. Letting  $\lambda_1$  = hazard ratio for time to first MACE for albiglutide vs placebo, then:

Null hypothesis:  $\log \lambda_1 \geq \log(1.3)$

Alternative hypothesis:  $\log \lambda_1 < \log(1.3)$

### **8.2. Study Design Considerations**

#### **8.2.1. Sample Size Assumptions**

The primary outcome will be analyzed such that the overall Type 1 error is no greater than 5% (two-sided). Specifically, the non-inferiority assessment of albiglutide compared to placebo will be conducted at 0.05 level, requiring one-sided significance at 0.025.

The power for MACE non-inferiority is calculated via the asymptotic variance and normality of the maximum likelihood estimator for the log-hazard ratio. Assuming a true hazard ratio of 1.0, 611 events will be needed to have 90% power to rule out non-inferiority margin of 1.3 for the hazard ratio with type I error of 0.05. The study duration will be event-driven. A total of 9400 subjects will be enrolled and followed until it is projected that approximately 611 adjudicated MACE events will have occurred. If the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years respectively, assuming that the number of subjects lost to follow-up accounts for 1% or less.

#### **8.2.2. Sample Size Sensitivity for MACE non-inferiority**

9400 subjects will be enrolled to cumulate the first MACE events experienced by 611 unique subjects. The study duration may vary depending on actual MACE event rate and duration of enrolment period.



**Table 2 Total Study Duration Sensitivity for Varying MACE Event Rate and Duration of Recruitment**

MACE rate (% pa)	Duration of recruitment			
	1.5 yrs	2.0 yrs	2.5 yrs	3.0 yrs
2.0	4.1yrs	4.4yrs	4.6yrs	4.9yrs
2.5	3.4 yrs	3.7yrs	3.9yrs	4.2yrs
3.0	3.0yrs	3.2yrs	3.5yrs	3.8yrs
3.5	2.7yrs	2.9yrs	3.2yrs	3.4yrs

**8.2.3. Sample Size Re-estimation**

The aggregate blinded event-rate data will be periodically reviewed by the Executive Committee and the sponsor. The study has an event-driven design. Should emerging data diverge significantly from protocol assumptions, the total sample size and/or follow up time may be adjusted, within the bounds of feasibility, to achieve the event target.

**8.3. Data Analysis Considerations****8.3.1. Analysis Populations**

The intent-to-treat (ITT) population will include all randomly assigned subjects. The ITT subjects will be analyzed according to randomised treatment. The inference for primary objectives in the study will be made from ITT population.

Per-protocol Population (PP) will exclude the subjects who have major protocol violations. Per-protocol analysis will include Per-protocol population only and their data upon to the time of discontinuation of investigational product plus 56 days.

The non-insulin population (NI) will include all subjects in the ITT population who are not on insulin at baseline. Inference for the time to insulin endpoint will be made from the NI population.

The baseline basal insulin user population (BI) will include all subjects in the ITT population who are on basal insulin, but not on other insulin at baseline. Inference for the time to prandial insulin endpoint will be made on BI population.

The safety population will include all enrolled subjects who receive at least 1 dose of study treatment. The safety population subjects will be analyzed according to the treatment received. The safety population will be used for analyses of safety objectives.

Other analysis populations will be defined in the RAP.

### **8.3.2. Analysis Data Set**

For time to event data, censoring time for subjects who lost to follow-up is defined as following:

- For primary analysis, subjects who are lost to follow-up will be censored at the date of last evidence of confirmatory status for MACE events.
- For on-treatment analysis, censoring date will be the last dose date.
- For on-therapy analysis (on-treatment+56 days), censoring date will be the last dose date+56 days.
- For analysis of all cause of mortality, censoring date will be the latest date known alive.

### **8.3.3. Treatment Comparisons**

Demographic and baseline characteristics (e.g., gender, age, racial or ethnic origin, height and weight, body mass index (BMI), blood pressure and other characteristics) will be summarized for each treatment group. In addition, smoking and alcohol habits, diabetic and cardiovascular medical history, baseline laboratory results, and prior medications will be summarized by treatment group. Binary and ordinal characteristics will be summarized by counts and percentages, while continuous variables will be represented by mean and standard deviations or medians and percentiles, as appropriate. Any variables with treatment imbalances may be considered as covariates for further analysis of an exploratory nature. Such covariates will be identified on the basis of the clinical relevance of the observed treatment difference.

#### **8.3.3.1. Primary Comparisons of Interest**

The primary endpoint will be the time to the first occurrence of MACE over the full duration of the study. A p-value for the primary endpoint will be calculated from a Cox regression model with treatment group as the only covariate for the hypotheses described in Section 8.1.

#### **8.3.3.2. Other Comparisons of Interest**

For other analyses incidence rates will be presented for binary data and summary statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous data. Furthermore, summary statistics of change from baseline for HbA1c will be presented along with percent of subjects within ranges of clinical interest (e.g., HbA1c < 7.0%).

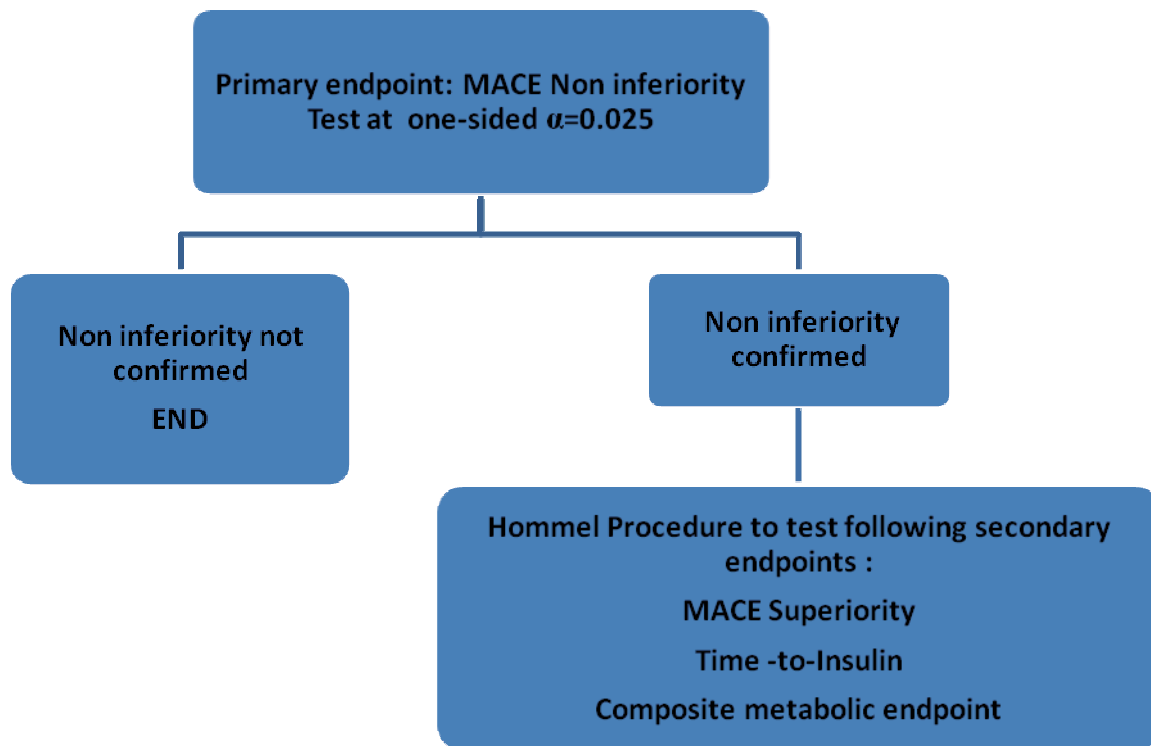
#### **8.3.4. Interim Analysis**

An IDMC will monitor progress of the study and ensure that it meets the highest standards of ethics and subject safety. All cardiovascular event data, together with other safety data, will be sent to the IDMC for review at approximately every 6 months after the first subject has been randomised to receive treatment. This frequency may be adjusted, if deemed necessary by the IDMC, depending on the enrolment rates and the rate of safety events. There are no plans to stop the study early for a non-inferiority or benefit claim, however should the IDMC identify in the course of its scheduled reviews overwhelming evidence of MACE benefit (e.g.,  $p < 0.001$ ), with directionally consistent findings on all-cause mortality, the IDMC might consider recommending early stopping. This approach essentially preserves the final alpha for the end-of-study analysis at 5% and hence there are no plans to adjust the final alpha on account on safety reviews conducted by the IDMC. The IDMC charter, reporting and procedures are outlined in separate documents.

#### **8.3.5. Multiplicity Controls**

A multiple comparisons adjustment strategy will be implemented for the multiple inferential tests among the primary endpoint and secondary endpoints of MACE superiority, time to insulin and composite metabolic endpoint.

The strategy will use a combination of gatekeeper and Hommel procedure. The first step is to evaluate the MACE non-inferiority of the albiglutide group vs the placebo group at a one-sided  $\alpha=0.025$  level. If the result of non-inferiority is significant, MACE superiority, time-to-insulin and composite metabolic endpoint will be tested simultaneously using the Hommel procedure with  $\alpha=0.05$ . The above multiplicity control approach will preserve the study's nominal significance level of 0.05. The test order is illustrated in the diagram below.



Hommel Procedure for secondary endpoints is described below:

Three hypothesis tests for MACE superiority, time-to-insulin, and composite metabolic endpoint are subject to be adjusted by the Hommel procedure. Let  $P(1)$ ,  $P(2)$  and  $P(3)$  represent the ordered p-values that  $P(3) > P(2) > P(1)$  and  $H(1)$ ,  $H(2)$  and  $H(3)$  are corresponding hypotheses.

If  $P(3) < 0.05$ , reject  $H(3)$ ,  $H(2)$ ,  $H(1)$ . End of test.

If  $P(3) \geq 0.05$  and  $P(2) < 0.05/2$ , accept  $H(3)$ , reject  $H(2)$ ,  $H(1)$ . End of test.

If  $P(3) \geq 0.05$  and  $P(2) \geq 0.05/2$  and  $P(1) < 0.05/3$ , accept  $H(3)$ ,  $H(2)$ , reject  $H(1)$ . End of test.

If  $P(3) \geq 0.05$ ,  $P(1) \geq 0.05/3$  and  $0.05/2 \leq P(2) < 0.05 \cdot 2/3$ , accept  $H(3)$ ,  $H(2)$ , reject  $H(1)$ . End of test.

If  $P(3) \geq 0.05$ ,  $P(2) \geq 0.05 \cdot 2/3$  and  $P(1) \geq 0.05/3$ , accept  $H(3)$ ,  $H(2)$  and  $H(1)$ .

#### *Other Secondary Endpoints and Subgroup Analysis*

The following secondary endpoints will provide supportive evidence for cardiovascular safety and will not use any multiplicity adjustment procedure.

- Components of primary endpoint (MACE = cardiovascular death, MI, stroke)
- MACE + urgent revascularisation for unstable angina
- Cardiovascular death or hospitalisation for heart failure

Other secondary endpoints which do not qualify for formal statistical hypothesis testing will be analyzed and have results presented with confidence interval and nominal p-values:

- Mean HbA1c at scheduled visits and change from baseline
- Mean body weight at scheduled visits and change from baseline
- Mean eGFR at scheduled visits and change from baseline
- Time to initiation of prandial insulin
- Composite microvascular endpoint

To examine the degree of consistency of the overall treatment effect in terms of important prognostic factors, subgroup analyses of the primary outcomes will be performed based on subject demographics and baseline characteristics. These exploratory subgroup analyses will not be adjusted for multiple comparisons and will be interpreted descriptively.

### **8.3.6. Key Elements of Analysis Plan**

Any deviations from the original analysis planned in the protocol agreed upon prior to finalization of the RAP, will be described in that document. Any additional changes to the planned analysis in the RAP will be described in the final clinical study report.

#### **8.3.6.1. Primary Analysis**

The primary analysis is an ITT analysis of the time to the first occurrence of MACE over the full duration of the study. Time to event analyses will be performed using Cox's Proportional Hazard regression with SAS PHREG with treatment group as the only covariate. Data for subjects without a primary event will be censored.

Treatment differences will be estimated via the hazard ratio and its 95% confidence interval (CI).

The hypothesis of non-inferiority of albiglutide relative to placebo group with hazard ratio less than 1.3 with respect to cardiovascular risk will be tested at the end of the study when ~611 first MACE events are cumulated.

The strength of evidence for non-inferiority will be determined by testing the hypothesis that the observed hazard ratio is significantly different from the null margin of 1.3 (one-sided  $p < 0.025$  for such a test being equivalent to the upper 95% confidence limit after multiplicity adjustment for the hazard ratio being less than 1.3). The absolute risk difference per 100 PY and superiority p-value for albiglutide vs. placebo will also be presented.

The product-limit estimates of the probabilities (and their standard errors) of first MACE over time will be computed and displayed as Kaplan-Meier (KM) survival curves for albiglutide and placebo groups. The KM curves will also be presented corresponding to the above comparisons.

The total number of all MACE or any of its components will be analyzed by Poisson regression model. The incidence rate per 100 person-years, relative risk and their 95% CI will be presented. Number of subjects who experienced at least one event, 2 or 3 or more MACE or its components will also be summarized by treatment group.

As sensitivity analyses, the analyses described above will be repeated using events occur while on-treatment and events occur during the period of on-treatment plus 56 days post last dose.

### **8.3.6.2. Secondary Endpoint Analysis**

Endpoints that supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes endpoints:

- MACE superiority will be evaluated using the same Cox regression model as the primary analysis of MACE non-inferiority.
- Supportive endpoints including the time to first occurrence of adjudicated MACE or urgent revascularisation for unstable angina, time to first occurrence of individual components of MACE, time to first occurrence of cardiovascular death or hospitalisation for heart failure will be analyzed using a proportional Cox regression model similarly as the primary endpoint.

Endpoints that evaluate the effects of albiglutide on metabolic management of type 2 diabetes:

- Among the subjects who are not on insulin at baseline (NI population), time to insulin will be analyzed using a proportional Cox regression model similar to the primary MACE analysis. The product-limit estimates of the probabilities (and their standard errors) of adding insulin over time will be computed and displayed as Kaplan-Meier (KM) survival curves for albiglutide and placebo treatment groups. The KM curves will also be presented corresponding to the above comparisons.
- Composite of the proportion of those achieving good control ( $HbA1c \leq 7.0\%$ ) AND no severe hypoglycaemic incidents AND weight gain  $<5\%$  at the end of the study would be evaluated utilize nonparametric, covariance-adjusted, extended Mantel-Haenszel tests. Additional analysis will be provided for scheduled visits. Nominal p-values and 95% CIs will be presented for these visits. Time to introduction of prandial insulin in those on basal insulin  $\pm$  orals anti-hyperglycemic drugs at baseline will be analyzed using PH model / log-rank test and KM method similar to the primary endpoint.
- Composite of microvascular events will be analyzed using a proportional Cox regression model / log-rank test and KM method similar to the primary endpoint.

- HbA1c, body weight and eGFR will be analyzed using a repeated mixed effect model. The least square means, 95% CIs and nominal p-values will be presented.
- Additional analysis will be performed to assess the incidence rate of recurrent severe hypoglycaemic events between treatment groups during the course of the study. A repeated Poisson regression model including treatment and visit as factors will be used to test treatment difference with offset for person years. An unstructured working correlation matrix will be used in the iterative estimation process. The model-adjusted least square incidence rate for each treatment as well as the treatment difference of the incidence rate will be reported. Events of severe hypoglycaemia will also be summarized descriptively by treatment group. Additional summary by baseline HbA1c, renal status and age subgroup will also be provided.

Further analysis details will be provided in the RAP.

#### **8.3.6.3. Subgroup Analysis**

Separate subgroup analyses of the primary outcomes will be performed based on subject demographics and baseline characteristics. Subgroups may include sex, age group, BMI, whether subjects have history of a previous cardiovascular event, and baseline HbA1C, background of anti-hyperglycaemia treatment etc. The detail of subgroups will be pre-specified in the RAP. Consistency of treatment effects will be assessed using Cox regression, along with the 95% confidence intervals for the relative risk or hazard ratios for each subgroup a nominal alpha level for interaction of 0.10 will be used. The effect of treatment interaction with subgroups will also be explored; however as the number of these subgroup variables may be large, the probability of observing at least one statistically significant result may be high. Thus these additional analyses will be considered exploratory regardless of the p-value associated with any interaction.

Further details will be provided in the RAP.

#### **8.3.6.4. Other Safety Analyses**

Subject demographics, medical history, prior and concomitant medications, vital sign measurements, laboratory values, physical examination assessments, will be summarized by treatment group using descriptive statistics.

For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages.

For SAEs, AEs leading to withdrawal and AEs of special interest occurring after discontinuation of investigational product, the number and percentage of subjects, total number of events, incidence density and event rate will be presented by treatment group and overall at the SOC, High Level Term and Preferred Term (PT) level. Relative Risk for each event and its 95% CI will also be presented. The time to first occurrence of the specific events and the time of the event with respect to the preceding dose of study medication will be summarized.

All cause mortality will be summarized by treatment group and analyzed using PH model similarly as the-primary endpoint.

All events sent to CEC (including TIAs) will be grouped by type based on the standard MedDRA queries that correspond to cardiovascular and cerebrovascular events. Adjudication results will be summarized by event type and treatment group. A by subject listing of these events will be generated. The listing will include seriousness, severity, whether event is a reason for early study drug discontinuation or study withdrawal, and adjudication results.

Pancreatitis events will be adjudicated by the independent Pancreatitis Adjudication Committee. The information for investigator reported pancreatitis events and its adjudication results will be provided.

Further analysis details will be provided in the RAP.

#### **8.3.6.5. Value Evidence and Outcomes Analyses**

TRIM-D total score and score for each domain will be summarized descriptively by treatment group and scheduled visit. Score changes from baseline will be compared between treatments for each visit by ANCOVA an model

For EQ-5D, subjects' responses at each visit for the 5 domains will be summarized categorically by treatment group, together with the summary of utility score at each visit and change from baseline by treatment group. Change from baseline will be compared between treatment groups for each visit by an ANCOVA model.

For study specific PRO questions, responses will be summarized descriptively by treatment group and scheduled visit.

Healthcare resource use will be summarized by treatment group and visit.

Further analysis details will be provided in the RAP.

## **9. STUDY CONDUCT CONSIDERATIONS**

### **9.1. Posting of Information on Publicly Available Clinical Trial Registers**

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



## **9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process**

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

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH E6 Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favourable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

Signed informed consent must be obtained for each subject prior to participation in the study

The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research. Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission. Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

## **9.3. Quality Control (Study Monitoring)**

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

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

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

#### **9.4. Quality Assurance**

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

#### **9.5. Study and Site Closure**

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

## **9.6. Records Retention**

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

## **9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication**

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

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

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.

### **9.8. Independent Data Monitoring Committee (IDMC)**

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter.

### **9.9. Pancreatitis Adjudication Committee**

Detailed information on suspected pancreatitis events will be collected on special pages of the eCRF. A Pancreatitis Adjudication Committee composed of independent specialists in gastroenterology will review cases of possible pancreatitis. Details of this committee and case adjudication are described in the committee's charter available on request.

## 10. REFERENCES

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## 11. APPENDICES

### 11.1. Appendix 1: Genetic Research

#### Background

Genetics is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of genetic associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	<i>HLA-B* 57:01</i> ( <i>Human Leukocyte Antigen B</i> )	Carriage of the <i>HLA-B*57:01</i> variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective <i>HLA-B*57:01</i> screening and exclusion of <i>HLA-B*57:01</i> positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labelling in the United States and Europe now recommend (US) or require (EU) prospective <i>HLA-B*57:01</i> screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. <i>HLA-B*57:01</i> screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.



Drug	Disease	Gene Variant	Outcome
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	<i>HLA-B*15:02</i>	Independent studies indicated that patients of East Asian ancestry who carry <i>HLA-B*15:02</i> are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of <i>HLA-B*15:02</i> prior to initiating treatment with carbamazepine.
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	<i>UGT1A1*28</i>	Variations in the <i>UGT1A1</i> gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular <i>UGT1A1</i> gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the <i>UGT1A1*28</i> variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful genetic research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable genetic analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to albiglutide.

### Genetic Research Objectives

The objective of genetic research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to albiglutide. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with albiglutide, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Safety and/or tolerability
- Efficacy

## Study Population

Any subject who is enrolled in the clinical study, can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from genetic research.

Subject participation in the genetic research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

## Study Assessments and Procedures

Blood samples can be taken for deoxyribonucleic acid (DNA) extraction and used in genetic assessments.

If taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (~6ml) will be collected for the genetic research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomised and provided informed consent for genetic research, but may be taken at any time while the subject is participating in the clinical study.

- The genetic sample is labelled (or “coded”) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilise the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct genetic analysis may be identified after a study (or a set of studies) of albiglutide has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to albiglutide.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

## Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in genetic research with the genetic sample retained for analysis
- Withdraw from genetic research and destroy the genetic sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time when a subject wishes to withdraw from genetic research or have their sample destroyed whether during the study or during the retention period following close of the main study.

## Screen and Baseline Failures

If a blood sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

## Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to albiglutide. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and genetic research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data.

Results of genetic investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

### **Informed Consent**

Subjects who do not wish to participate in genetic research may still participate in the clinical study. Genetic informed consent must be obtained prior to any blood being taken for genetic research.

### **Provision of Study Results and Confidentiality of Subject's Genetic Data**

GSK may summarise the genetic research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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## 11.2. Appendix 2: GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

1. Contraceptive subdermal implant that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label.
2. Intrauterine device or intrauterine system that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Trussell, 2011]
3. Oral Contraceptive, either combined or progestogen alone [Trussell, 2011]
4. Injectable progestogen [Trussell, 2011]
5. Contraceptive vaginal ring [Trussell, 2011]
6. Percutaneous contraceptive patches [Trussell, 2011]
7. Male partner sterilization prior to the **female subject's entry** into the study, and this male is the sole partner for that subject. The information on the male sterility can come from interview with the subject on her male partner's medical history.
8. Male condom **combined with a female** diaphragm, with or without a vaginal spermicide (foam, gel, film, cream, or suppository). In the UK it is a country-specific requirement of the regulatory authority (Medicines and Healthcare Products Regulatory Agency) that a vaginal spermicide be used.

These allowed methods of contraception have a failure rate of less than 1% per year but are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

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### 11.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

**Phase III-IV liver chemistry stopping and increased monitoring criteria** have been designed to assure subject safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).

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

#### Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
<b>ALT-absolute</b>	ALT $\geq$ 8xULN
<b>ALT Increase</b>	ALT $\geq$ 5xULN but <8xULN persists for $\geq$ 2 weeks ALT $\geq$ 3xULN but <5xULN persists for $\geq$ 4 weeks
<b>Bilirubin<sup>1, 2</sup></b>	ALT $\geq$ 3xULN <b>and</b> bilirubin $\geq$ 2xULN (>35% direct bilirubin)
<b>INR<sup>2</sup></b>	ALT $\geq$ 3xULN <b>and</b> INR>1.5, if INR measured
<b>Cannot Monitor</b>	ALT $\geq$ 5xULN but <8xULN and cannot be monitored weekly for $\geq$ 2 weeks ALT $\geq$ 3xULN but <5xULN and cannot be monitored weekly for $\geq$ 4 weeks
<b>Symptomatic<sup>3</sup></b>	ALT $\geq$ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> <li>Immediately discontinue study treatment</li> <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 subject until liver chemistries resolve, stabilize, or return to within baseline (see <b>MONITORING</b> below)</li> <li><b>Do not restart</b> subject with study treatment unless allowed per protocol and GSK Medical Governance approval <b>is granted</b> (refer to</li> </ul>	<ul style="list-style-type: none"> <li>Viral hepatitis serology<sup>4</sup></li> <li>Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody<sup>5</sup>.</li> <li>Blood sample for pharmacokinetic (PK) analysis, obtained within 3 half lives (15 days) of last dose<sup>6</sup></li> <li>Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</li> <li>Fractionate bilirubin, if total bilirubin <math>\geq</math> 2xULN.</li> </ul>

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<p><a href="#">Appendix 5</a>)</p> <ul style="list-style-type: none"> <li>• <b>If restart is not granted</b>, permanently discontinue study treatment and continue subject in the study for any protocol specified follow up assessments</li> <li>• Re-challenge is not allowed.</li> </ul> <p><b>MONITORING:</b></p> <p><b><u>For bilirubin or INR criteria:</u></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 hrs</b></li> <li>• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline</li> <li>• A specialist or hepatology consultation is recommended</li> </ul> <p><b><u>For All other criteria:</u></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> </ul> <p>Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline</p>	<ul style="list-style-type: none"> <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, other over the counter medications.</li> <li>• Record alcohol use on the liver event alcohol intake case report form</li> </ul> <p><b><u>For bilirubin or INR criteria:</u></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 pressure liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [<a href="#">James</a>, 2009]). <b>NOTE: not required in China</b></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 subject if ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN (>35% direct bilirubin) or ALT  $\geq$  3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

### Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
<p>ALT <math>\geq</math>5xULN and &lt;8xULN <b>and</b> bilirubin &lt;2xULN <b>without</b> symptoms believed to be related to liver injury or hypersensitivity, <b>and</b> who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT <math>\geq</math>3xULN and &lt;5xULN <b>and</b> bilirubin &lt;2xULN <b>without</b> symptoms believed to be related to liver injury or hypersensitivity, <b>and</b> who can be monitored weekly for 4 weeks.</p>	<ul style="list-style-type: none"> <li>• Notify the GSK medical monitor <b>within 24 hours</b> of learning of the abnormality to discuss subject safety.</li> <li>• Subject can continue study treatment</li> <li>• Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline</li> <li>• If at any time subject meets the liver chemistry stopping criteria, proceed as described above</li> <li>• If ALT decreases from ALT <math>\geq</math>5xULN and &lt;8xULN to <math>\geq</math>3xULN but &lt;5xULN, continue to monitor liver chemistries weekly.</li> <li>• If, after 4 weeks of monitoring, ALT &lt;3xULN and bilirubin &lt;2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.</li> </ul>

**References**

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#### 11.4. Appendix 4: Liver Safety Drug Restart Guidelines

If subject meets liver chemistry stopping criteria do not restart subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the subject

If GSK Medical Governance approval to restart the subject with study treatment **is not granted**, then the subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

##### ***Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment***

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury) or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section [6.2.2](#) and [Appendix 5](#)

## **11.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events**

### **11.5.1. Definition of Adverse Events**

<b>Adverse Event Definition:</b>
<ul style="list-style-type: none"><li>• An AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</li><li>• NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.</li></ul>



<b>Events <u>meeting</u> AE definition include:</b>
<ul style="list-style-type: none"><li>• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.</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 prior to the start of the study.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).</li><li>• The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.</li></ul>

**Events NOT meeting definition of an AE include:**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

**11.5.2. Definition of Serious Adverse Events**

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, etc).

**Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:**

**c. Results in death****d. Is life-threatening**

NOTE:

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

**e. Requires hospitalization or prolongation of existing hospitalization**

NOTE:

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

**f. Results in disability/incapacity**

## NOTE:

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

**g. Is a congenital anomaly/birth defect****h. Other situations:**

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

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

- $ALT \geq 3 \times ULN$  and total bilirubin\*  $\geq 2 \times ULN$  (>35% direct), **or**
- $ALT \geq 3 \times ULN$  and  $INR^{**} > 1.5$ .

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

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

### 11.5.3. Recording of AEs and SAEs

#### AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.



#### 11.5.4. Evaluating AEs and SAEs

##### Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

##### Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

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

**11.5.5. Reporting of SAEs to GSK****SAE reporting to GSK via electronic data collection tool**

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor or the SAE coordinator
- Site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

## **11.6. Appendix 6: Collection of Pregnancy Information**

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, 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 5](#). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

### **Any female subject who becomes pregnant while participating**

- will discontinue study medication

## **11.7. Appendix 7: Electronic Health Record Ancillary Study**

### **11.7.1. Introduction**

#### **11.7.1.1. Background**

Clinical researchers and policy makers want to move towards embedding clinical trials directly within health care delivery systems in order to increase the relevance, speed, and efficiency of clinical research [Richesson, 2013]. The assumption is that the capabilities offered by Electronic Health Records (EHRs), along with concurrent changes in health care organization and delivery, and the development of a learning health system will transform the way clinical research is conducted [Etheredge, 2007; Greene 2007].

In 2011, the National Heart, Lung, and Blood Institute (NHLBI) convened the NHLBI Working Group on Electronic Health Records: Research Priorities to Improve Cardiopulmonary Health in Clinical Practice. As part of their mission, this working group identified key research, policy, and training priorities [Curtis, 2014]. A key research priority was to leverage EHR tools to facilitate the efficient implementation of randomized clinical trials. Specific areas highlighted for increased efficiency included efficient data collection and outcome surveillance and confirmation.

#### **11.7.1.2. Literature Review**

Electronic Health Records were primarily designed to document patient care and facilitate billing and reimbursement. The large amount of electronic data that are captured may also facilitate clinical research and public health surveillance.<sup>5</sup> Despite the complexity of EHR data, national networks have begun to use these data to improve public health and generate real-world evidence [Toh, 2012]. The Patient Centered Outcomes Research network (PCORnet) (pcornet.org) is a research network that is currently being designed to support observational comparative effectiveness research and clinical trials that are embedded in clinical care settings [Fleurence, 2014]. Similarly, the NIH Health Care Systems Research Collaboratory (nihcollaboratory.org) is creating infrastructure to improve the conduct of embedded clinical trials. One ongoing NIH Collaboratory trial is the Time to Reduce Mortality in End-Stage Renal Disease study (TiME) (clinicaltrials.gov identifier: NCT02019225). TiME is a large cluster-randomized, pragmatic trial that will evaluate the effects of systematic implementation of hemodialysis sessions of at least four hours versus usual hemodialysis care. The trial involves data acquisition from EHR systems through a partnership between academic investigators and two health care provider organizations with different electronic data systems. There are several other recent examples of clinical trials that were embedded in health care delivery systems [Gulliford, 2014; van Staa, 2014]. For instance, one recent study evaluated the use of an electronic decision support tool to improve risk factor control (i.e., blood pressure and cholesterol) following a cerebrovascular event with outcome data collected from the EHR [Dregan, 2014]. While the specific intervention was not shown to be efficacious, data acquisition via EHR sources was robust and implemented at a low cost.

### 11.7.1.3. Ancillary Study Rationale

Despite these earlier studies demonstrating the potential opportunities with EHR-based data acquisition, our understanding of how EHR-based platforms might increase the efficiency of data collection, outcome surveillance, and confirmation in an integrated manner is unknown. EHRs are inherently heterogeneous, with each implementation different from the next. The barriers to using EHR-generated lists of patients to facilitate trial enrolment, the fitness of EHR data for populating baseline characteristics in an electronic case report form (eCRF) and the use of EHR data to find events of interest during trial follow-up are not well characterized.

EHR systems contain a wealth of clinical data about patients who are connected to the health care delivery system and may be eligible for enrollment in a clinical trial. Anecdotal reports suggest that identification of potential patients using the EHR increases the number of patients to be screened but may not consistently translate to an increased number of patients enrolled. Causes are likely multi-factorial and may include the translatability of inclusion and exclusion criteria to structured clinical data, the algorithm used to identify potential patients, institutional restrictions regarding unsolicited patient contact, and others. There is a need to empirically assess the barriers to using an EHR-generated list of patients to facilitate trial enrollment.

Structured data captured in the EHR may be similar to data elements specified in baseline patient characteristics in the eCRF, yet EHR data are collected primarily to support clinical care and reimbursement needs. Their fitness for use as source data for selected data elements of the baseline patient characteristics in the eCRF has not been established.

During routine trial follow-up, study coordinators typically gather information from various sources including direct patient contact and medical records of the enrolling institution and outside facilities to document events for study participants. Evidence from the West of Scotland Coronary Prevention Study suggests that cardiovascular endpoints can be ascertained from routinely recorded EHR-type data, but classification was imperfect [Barry, 2013]. There is a need to specifically assess the utility of EHR data acquisition for follow-up events across multiple health systems.

In summary, the EHR is a rich source of clinical data, but is designed specifically to support clinical care delivery and reimbursement needs. The assumption that EHR data are fit for use in high-quality clinical research has not been rigorously evaluated. To provide evidence to address this knowledge gap, GlaxoSmithKline (GSK) and Duke Clinical Research Institute (DCRI) are committed to conducting an exploratory EHR Ancillary Study embedded within a large pragmatic clinical trial at selected study sites. The overarching goal is to further our understanding of how EHR data can be organized into a query-able format to facilitate a more efficient, reliable, and cost-effective research process. The proposed empirical work is exploratory in nature and both qualitative and quantitative.

## **11.7.2. Ancillary Study OBJECTIVES**

### **11.7.2.1. Primary Objectives**

#### **Objective 1: Assess the barriers to using an EHR-generated list of patients to facilitate trial enrollment.**

Through site study coordinator surveys, workflow assessment, analysis of electronic screening logs, comparisons of enrolled patients with patients identified via algorithm, this retrospective objective will describe the screening “funnel” and identify factors responsible for narrowing the funnel from the pool of potentially eligible patients to those enrolled in the clinical trial. Barriers for using EHR systems for this purpose will be assessed at the site level and common cross-site themes will be identified.

#### **Objective 2: Evaluate the fitness of EHR data for use in populating the baseline characteristics in the eCRF**

After study completion and within selected data areas (e.g., demographics, medical history, concomitant medications), the level of agreement between data extracted from the EHR and data documented on the baseline eCRF (reference standard) will be evaluated. Additionally the performance of algorithms developed to identify comorbidities and other clinical concepts will be assessed at the site level and aggregated, where appropriate.

#### **Objective 3: Explore the use of EHR data to find events of interest during trial follow-up**

Case-finding algorithms will be developed for select specified endpoints (i.e., myocardial infarction, stroke, unstable angina, heart failure as outlined in the main study protocol), run during the conduct of the trial, and used to identify potential cases for follow-up by the study coordinator. The site study coordinator will record the dispensation of each potential case so that reconciliation can occur between eCRF documented events and EHR-generated potential events. Safety event reporting will proceed as outlined in the main study protocol (Main Protocol Section 6.2). At the conclusion of the study, the yield of case-finding algorithms will be evaluated along with the performance of EHR-based algorithms with eCRF-reported as well as adjudicated eCRF-reported events (reference standard).

### **11.7.2.2. Secondary Objective**

As a secondary objective, an assessment of the general utility and feasibility of EHR-based outcome acquisition from the coordinator perspective through surveys and standardized workflow assessments will be conducted.

### **11.7.3. Ancillary Study design**

#### **11.7.3.1. Study Design**

The ancillary study will occur in the context of the HARMONY-Outcomes trial, a randomised, double blind, parallel-group, placebo-masked, controlled study to evaluate the effect of albiglutide on cardiovascular events in patients with Type 2 diabetes. Albiglutide will be administered subcutaneously once weekly in a population of patients with Type 2 diabetes and a previous history of cardiovascular disease and who do not have optimal glycaemic control). The duration of the ancillary study will mirror that of the HARMONY-Outcomes trial. The number of sites that will participate in the ancillary study depends upon the outcome of the site EHR capabilities assessment described in Section [11.7.3.2](#) (Site Selection) below. Five study sites recruiting 12-15 subjects each would enable a descriptive assessment of Objectives 1 and 2, whilst, if feasible, 500-1000 subjects at EHR-enabled sites would permit greater precision to be achieved in the assessment of Objective 3.

#### **11.7.3.2. Site Selection**

Sites from the main trial will be selected to participate. As part of the overall site selection process for the main trial, potential sites complete a feasibility survey to gauge their suitability for participation in the HARMONY-Outcomes trial. In addition to questions regarding experience with long-term outcome trials in general and specific features of the planned trial, the feasibility survey includes questions about site readiness for an EHR-facilitated trial. Specific topics include:

- Existence of an EHR system;
- Current use of EHR to screen for potential study participants;
- Types of information currently contained in EHR (inpatient visits, outpatient visits, laboratory results, medications)
- Prior participation in a study that used EHR data for patient screening, follow-up, and/or data collection; and
- Local EHR support to assist with research studies.

Sites who meet minimum qualifications based on this survey (respond affirmatively regarding the existence of an EHR system and local EHR support to assist with research studies), and who have confirmed an interest in participating in the ancillary study will be approached for a more in-depth assessment of capabilities. Specific topics include:

- Current capability to extract EHR-type data from a data warehouse;
- Data domains currently included in the data warehouse (e.g., demographics, vital signs, diagnoses, procedures, medications prescribed, laboratory tests, and death);

- Coding terminologies used for each domain of data;
- Institutional processes and policies for using EHR-type data for clinical research;
- Institutional experience extracting, transforming, and loading warehouse data into a research DataMart that conforms with standardized specifications; and
- Familiarity with or participation in distributed research networks.

Subsequent structured discussions with individual sites may be necessary to explore capabilities and suitability for the ancillary study. For example, engagement of the health system's Information Technology (IT) personnel will be essential but is challenging to gauge in a written survey. Key site selection criteria include:

- Fully implemented EHR system
- Access to an enterprise data warehouse or clinical data repository that stores structured data from the EHR and is updated at least weekly.
- Availability of necessary data
- Engagement of health system IT and analytical personnel

The advantage of a multi-stage, rapid assessment of capabilities is that it allows for a relatively short feasibility survey that can be completed reliably by a study coordinator. Detailed technical questions are reserved for the individuals who provide EHR support for research studies.

#### **11.7.3.3. Data Flows**

The methods for data extraction and capture will require a partnership between study site teams (site principal investigator, site study coordinator, and site technical support), GSK, and the DCRI Data Management Team.

The study will utilize PopMedNet, a software application that enables the creation, operation, and governance of research networks. It allows partners to maintain physical and operational control over their data while allowing authorized users to send queries to the data. PopMedNet consists of two layers: a security layer where access controls and permissions are established and a layer of virtual pipes through which questions are sent from requestor to responder. The PopMedNet software consists of a web-based "network portal" and a DataMart Client application that is installed at each site. PopMedNet employs a "publish-and-subscribe" architecture that does not require a hole through an institutional firewall, but rather allows institutions to pull a query behind the firewall for manual or automated execution.

In research networks with a common data model, PopMedNet is used to distribute executable code that institutions can choose to pull behind their firewall, run against the data in that appropriate format, and return results to the requestor. Security documentation will be provided to all participating sites.



The data flow for this ancillary study will be as follows:

- a) The study site's EHR system will not be changed and will continue to operate as implemented. Data from the thousands of tables in the EHR will be integrated on a nightly basis into a data warehouse that supports research needs (the term EHR is used to mean the system that collects, displays, and stores transactional health care data).
- b) With guidance from the DCRI Data Management Team, the study site's technical team will extract, transform, and load data from the enterprise data warehouse (or clinical data repository) to a Cohort DataMart according to the specifications of the common data model. A common data model standardizes the definition, content and format of data across sites to enable efficient, cross-site querying. The Cohort DataMart will be refreshed from the existing Data Warehouse on a biweekly basis. The Cohort DataMart includes Protected Health Information (PHI) for a broadly defined cohort of potential study participants and will remain behind institutional firewalls.
- c) Data from Pre-Screening logs completed as part of the main study will be captured in a database stored in the same area as the Cohort DataMart to facilitate characterization of the screening funnel. Data from the pre-screening log will enable comparisons of characteristics of potential participants identified via algorithm with patients screened and enrolled.
- d) When a participant is randomized into the study, the study coordinator will enter key subject identifiers (the main trial identifier (ID), Medical Record Number (MRN) equivalent, study randomization date) into the Key Identifier spread sheet.
- e) Via PopMedNet, the DCRI Data Management Team will distribute code that extracts data for randomized participants from the Cohort DataMart into the Study DataMart using the Key Identifier table. Trial ID and randomization date from the Key Identifier table will be included in the Study DataMart. Data for randomized patients at each site will be returned to the DCRI via the HARMONY-Outcomes trial EHR Ancillary Study Query Portal.
- f) Via PopMedNet, the DCRI will distribute executable code (e.g., SQL program) that will query the Study DataMart for potential study endpoints. [See Section [11.7.3.4.1b](#) for case-finding algorithm].
- g) Potential cases (identified via case-finding algorithm) will be returned to the Study Coordinator who will record the dispensation of each potential case in the Case-finding Dispensation Log stored in the Study DataMart (i.e., recorded in the eCRF/not recorded in the eCRF and reasons).
- h) The Study DataMart containing randomized patient data will be transferred from each site to the DCRI on a regular basis (anticipated quarterly with specific frequency to be determined).
- i) Required data elements from the main clinical trial dataset for EHR Ancillary Study sites will be transferred from GSK to the DCRI after the completion of the study. The DCRI will merge data elements from the main clinical trial dataset with Study DataMart data to create the EHR Ancillary Study Dataset.

#### **11.7.3.4. Study Procedures and Processes**

##### **11.7.3.4.1. DCRI**

###### **a) Establish broad definition of cohort**

A broad cohort identification algorithm will be developed based on selected inclusion criteria outlined in the main study protocol. Selected criteria for inclusion into the cohort include:

- Age > 40 years old
- Diagnosis of Type 2 diabetes, broadly defined by diagnosis codes and medications prescribed (See 4.4 for information about algorithms to be used.)
- Established cardiovascular disease (See Section 11.7.4.4 for information about algorithms to be used)

Participating sites will be required to run the “cohort algorithm” within their EHR systems to create the Cohort DataMart which will be used as a basis for Objective #1.

###### **b) Specify contents of the EHR Ancillary Study research DataMart**

EHR data are stored in many different ways. A common data model standardizes the definition, content and format of data across sites to enable a single standardized view that can be used for querying. Sites participating in this ancillary study will be required to transform their data into a common data model that will be designed to be intuitive and user-friendly. Investigators and analysts with prior experience using research data will not need additional skills or knowledge to use the common data model. The DCRI team will manage questions and issues that arise regarding transforming data into the CDM.

The EHR Ancillary Study Common Data format will be adapted from the Patient Centered Outcomes Research Network (PCORnet) Common Data Model (<http://pcornet.org/resource-center/pcornet-common-data-model/>) and may include the following data areas:

- Demographic
- Encounter
- Diagnosis
- Procedure
- Medications prescribed
- Laboratory results, selected

**c) Develop data characterization routines**

As previously described, participating sites will transform local data into the study common data model. The DCRI Data Management Team will develop and distribute code to query the content of tables formatted according to the common data model. The distributed code will generate aggregate output tables that help determine whether the data conform to specifications, maintain integrity across variables and across tables, and trend as expected over time. The data quality review and characterization process will help to ensure that the data meets reasonable standards for data transformation consistency and quality.

DCRI's team will evaluate the creation of the Cohort DataMart using standard programs distributed to each study site for execution behind institutional firewalls.

**d) Develop and distribute test queries**

A series of simple test queries will be developed and distributed to sites for execution against a simulated data set, structured according to the common data model. The test queries will help each site become familiar with PopMedNet and distributed querying without concern about querying against protected health information.

**e) Develop algorithms for analytic variables**

Algorithms to map EHR-based data in the Study DataMart to baseline characteristics and study endpoints in the EHR Ancillary Study dataset will be defined using diagnosis codes (ICD-9-CM and ICD-10-CM) and procedure codes (ICD-9-CM and ICD-10-PCS). Published algorithms will be used whenever possible. Examples of published algorithms utilized in the past include:

- CMS chronic condition categories: <https://www.ccwdata.org/web/guest/condition-categories>
- Quan, H., Sundararajan, V., Halfon, P., Fong, A., Burnand, B., Luthi, J. C., ... & Ghali, W. A. (2005). Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care*, 1130-1139. <http://www.ncbi.nlm.nih.gov/pubmed/16224307>
- Elixhauser, A., Steiner, C., Harris, D. R., & Coffey, R. M. (1998). Comorbidity measures for use with administrative data. *Medical Care*, 36(1), 8-27. <http://www.ncbi.nlm.nih.gov/pubmed/9431328>

These algorithms will be updated as necessary to account for coding changes since publication. And, if not provided, mapping of diagnosis codes from ICD-9-CM to ICD-10-CM and mapping of procedure codes from ICD-9-CM to ICD-10-PCS will be done using the general equivalence mappings provided by Centers for Medicare & Medicaid Services (CMS):

- Diagnosis code crosswalk: <http://www.cms.gov/Medicare/Coding/ICD10/2014-ICD-10-CM-and-GEMs.html>

- Procedure code crosswalk: <http://www.cms.gov/Medicare/Coding/ICD10/2014-ICD-10-PCS.html>

Algorithms used to identify specific medications dispensed will be defined using different drug identification coding systems in use by study sites. These systems could include:

- NDC codes [from RxNav, a browser for drug information available from the U.S. National Library of Medicine]
- DIN codes [from Health Canada drug product database]
- ATC codes [from WHO Collaborating Centre for Drug Statistics Methodology]

#### **11.7.3.4.2. Sites**

Participating study sites will:

- Extract, transform, and load (ETL) data into a physical instance of an adapted PCORnet Common Data Model. Sites will document the mapping from the EHR to the Common Data Model.
- Install PopMedNet
- Refresh the Cohort DataMart on a biweekly basis
- Execute data characterization and test queries after each refresh and on an as-needed basis.

Site study coordinators will be required to complete pre-screening logs on all potential study participants meeting minimum eligibility requirements (age >40, Type 2 diabetes, established cardiovascular disease) identified via any mechanism (i.e., reviewing lists of scheduled office patients, reviewing lists of recently discharged diabetes patients, EHR-facilitated algorithm). Pre-screening logs will capture the following information:

- Pre-screening number
- Pre-screening date
- Inclusion criteria not met
- Exclusion criteria met
- Other criteria

Site study coordinators will complete a screening survey which will describe the site's current process for screening. A description of screening barriers will be included.

## 11.7.4. DATA ANALYSIS

### 11.7.4.1. Sample Size Expectations

The objectives of this ancillary study are exploratory (not confirmatory) in nature and not intended to be sufficiently powered to confirm a pre-determined level of sensitivity and specificity. The number of sites and subjects that will participate in the ancillary study depends upon the outcome of the site EHR capabilities assessment described in Section 11.7.3.2 (Site Selection). Five study sites recruiting 12-15 subjects each would enable a descriptive assessment of Objectives 1 and 2, whilst, if feasible, 500-1000 subjects at EHR-enabled sites would permit greater precision to be achieved in the assessment of Objective 3.

### 11.7.4.2. Objective 1: Assess the Barriers to Using as EHR-Generated List of Patients to Facilitate Trial Enrollment

Because any survey administered for this objective will be a site-level survey, analysis of the survey data will be performed across all sites. For quantities of interest, frequencies with percentages for categorical measures and means with standard deviations for continuous measures will be presented.

### 11.7.4.3. General Analytic Approach for Objective 1 and Objective 2

The goals of both Objective 2 and Objective 3 involve evaluating the performance of algorithms that map EHR-based data into concepts present in the clinical trial dataset. The actual measures recorded in the clinical trial dataset will be considered the reference standard against which these algorithm-based measures are compared.

**Table 3 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Categorical variables**

New measure (EHR Ancillary Study data)	Reference standard (Clinical trial data)	
	Condition present	Condition absent
Condition present	True positive (TP)	False positive (FP)
Condition absent	False negative (FN)	True negative (TN)

For categorical variables, estimated performance metrics will be based on the 2x2 cross-tabulation of values in the EHR Ancillary Study dataset with values in the clinical trial dataset (Table 3) and include:

- Overall agreement =  $(TP + TN) / (TP + FP + FN + TN)$
- Sensitivity =  $TP / (TP + FN)$

- Specificity =  $TN / (FP + TN)$
- Positive predictive value =  $TP / (TP + FP)$
- Negative predictive value =  $TN / (FN + TN)$
- Accuracy or efficiency =  $(TP + TN) / (TP + TN + FP + FN)$

For dichotomous measures, each of these proportions is immediately calculable. For measures having more than two levels, multiple dichotomous measures will be created in order to calculate these proportions. Confidence intervals (95%) will be reported around these quantities. (See [Table 4](#) as an example).

**Table 4 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Categorical variables**

Measure	Overall agreement (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Measure 1	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
Measure 2	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
.....	.....	.....	.....	.....	.....

Reported on 0–100 scale

For continuous measures, bias will be calculated as the difference between values in the EHR Ancillary Study dataset and values in the clinical trial dataset. The mean and standard deviation of the bias along with a 95% confidence interval will be reported. In Bland-Altman analyses of agreement between continuous measures, the standard deviation of the bias is referred to as the precision, while the 95% confidence interval is referred to as the limit of agreement. (See [Table 5](#) as an example).

**Table 5 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Continuous variables**

Measure	Bias	
	Mean (SD)	95% (CI)
Measure 1	xx.x	xx.x
Measure 2	xx.x	xx.x
.....	.....	.....

Due to the nature of EHR data, it is expected that there will be systematic differences between sites with respect to coding of clinical concepts. All performance metrics will

therefore initially be calculated by site. These site-specific results may be best reported graphically.

There is also interest in an assessment of algorithm performance across all sites. Hierarchical models will be used to combine data from all sites and estimate performance at the “average” site. To estimate proportions (e.g. for overall agreement, sensitivity, specificity, etc. associated with categorical measures), models will be specified as:

$$\begin{aligned} \text{logit}(E(y)) &= \beta_0 + \gamma_{0,j} \\ \gamma_{0,j} &\sim N(0, s^2) \end{aligned}$$

where sites are indexed by  $j$ . The value of the proportion at the average site—when  $\gamma_0=0$ —is  $[1 + \exp(-\beta_0)]^{-1}$ . Patients included in the estimation of each model vary by performance metric and reflect the definitions above. As an example, consider positive predictive value. To estimate the positive predictive value of an algorithm, only subjects with true positive value and false positive values will be included. True positives will be assigned  $Y=1$  and false positive will be assigned  $Y=0$ .

To estimate means (e.g. for bias associated with continuous variables), the model will be specified as:

$$\begin{aligned} E(y) &= \beta_0 + \gamma_{0,j} \\ \gamma_{0,j} &\sim N(0, s^2) \end{aligned}$$

The value of the mean at the average site is  $\beta_0$ .

For all models, we will assess site heterogeneity by testing if  $s^2=0$ .

#### **11.7.4.4. Objective 2: Evaluate the Fitness of EHR Data for Use in Populating the Baseline Characteristics in the eCRF**

Algorithms will be defined to map EHR-based data in the Study Data Mart to specific concepts in the EHR Ancillary Study dataset that parallel concepts in the clinical trial dataset. For Objective 2, the performance of algorithms used to identify baseline characteristics will be evaluated. The baseline characteristic measures recorded in the clinical trial dataset will be considered the reference standard against which these algorithm-based measures are compared.

#### **11.7.4.5. Objective 3: Explore the Use of EHR Data to Find Events of Interest During Trial Follow-up**

Algorithms will be defined to map EHR-based data in the Study Data Mart to specific concepts in the EHR Ancillary Study dataset that parallel concepts in the clinical trial dataset. For Objective 3, the performance of algorithms used to identify trial events will be evaluated. These algorithms will be evaluated against both the adjudicated events recorded in the clinical trial dataset and the identified potential events in the eCRF. For each event, estimates of sensitivity and positive predictive value (described in Section [11.7.4.3](#)) will be calculated and presented with 95% confidence intervals.

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## **11.8. Appendix 8: Country Specific Requirements**

## **11.9. Appendix 9: Protocol Amendment Changes**

### **11.9.1. Changes Resulting from Protocol Amendment 1**

This amendment is applicable to all participating countries.

#### **Summary of Changes**

1. Correction of typographical error in Exclusion criterion 7.
2. Clarification wording added to the description of when subjects should have telephone follow-up after discontinuing investigational product (IP). Subjects should have the telephone follow-up  $5 \pm 1$  weeks after their last dose of IP whether they had continued IP through to the Final study visit, or discontinued before the Final study visit.
3. Time and Event Table modified to add adverse event checking (SAE, AEs of special interest, AEs leading to IP discontinuation) to dose adjustment visits, and to correct footnote assignment/typographical errors.
4. Revision of terminology used to describe unstable angina events referred for CEC adjudication to correctly reflect review process to be adopted by CEC.
5. Addition of Country Specific Requirements appendix (Appendix 8).

#### **List of Specific Changes**

Section 4.2, Exclusion criteria; criterion 7, fourth sentence.

*Original text:*

Women who have developed spontaneous secondary amenorrhoea of 12 months or more where post-menopausal status is in doubt, a blood sample where FSH >40MU/ml and oestrodiol <40 pg/mL (<14 pmol/L) are simultaneously measured will be considered confirmatory.

*Amended text:*

Women who have developed spontaneous secondary amenorrhoea of 12 months or more where post-menopausal status is in doubt, a blood sample where FSH >40MU/ml and oestrodiol <40 pg/mL (<14~~0~~ pmol/L) are simultaneously measured will be considered confirmatory.

Section 4.5 Procedures for Subject Follow-up*Original text:*

As described in Section 4.4, subjects who permanently discontinue investigational product will be asked to attend the clinic as soon as possible. They will continue in the study for follow-up. They will be asked to return to clinic according to the 8 monthly visit schedule and in addition be contacted by telephone at a time corresponding to the 4-monthly visit they would have otherwise made to replenish study medication supply. If instead of these interim telephone contacts the subject prefers to attend clinic every 4 months as originally scheduled that is an acceptable alternative.

*Amended text:*

As described in Section 4.4, subjects who permanently discontinue investigational product will be asked to attend the clinic as soon as possible. They will continue in the study for follow-up. ***Five weeks ( $\pm 1$  week) after discontinuation of investigational product, subjects will be contacted for a follow-up by telephone.*** They will be asked to return to clinic according to the 8 monthly visit schedule and in addition be contacted by telephone at a time corresponding to the 4-monthly visit they would have otherwise made to replenish study medication supply. If instead of these interim telephone contacts the subject prefers to attend clinic every 4 months as originally scheduled that is an acceptable alternative.

Table 1 Time and Events Table

*Original text:*

Procedures <sup>1,2</sup>	Screening <sup>2</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post and.)	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	Post-Study Follow up Phone Call 5 ± 1 weeks after last IP dose
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X		X	X	X

1. Subjects who discontinue investigational product should be handled as described in Section 4.4.

11. Study drug dispensing not performed at final visit, compliance check not performed at Screening.

*Amended text:*

Procedures <sup>1,2</sup>	Screening <sup>3</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post <i>rand.</i> )	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	<del>Post-Study</del> Follow up Phone Call 5 ± 1 weeks after last IP dose
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X	X	X	X	X

1. Subjects who discontinue investigational product should be handled as described in Section 4.4 **and Section 4.5**.

11. Study drug dispensing not performed at final visit, compliance check not performed at **Randomisation**.

### Section 6.2.1 Cardiovascular Events

#### *Original text:*

The CEC will review and adjudicate the following clinical events:

- Myocardial infarction
- Stroke
- Unstable angina requiring revascularization
- Hospitalization for heart failure
- Sudden cardiac death
- TIA
- In addition, all clinical events submitted for adjudication and all other SAEs with a fatal outcome will be reviewed and adjudicated to classify the cause of death as cardiovascular or non-cardiovascular.

#### *Amended text:*

The CEC will review and adjudicate the following clinical events:

- Myocardial infarction
- Stroke
- ***Unstable angina requiring hospitalization***
- Hospitalization for heart failure
- Sudden cardiac death
- TIA
- In addition, all clinical events submitted for adjudication and all other SAEs with a fatal outcome will be reviewed and adjudicated to classify the cause of death as cardiovascular or non-cardiovascular.

### Appendix 8 – Country Specific Requirements

Appendix 8 added (not in original text). This is a blank page headed “11.8. Appendix 8: Country Specific Requirements” to serve as a placeholder to be replaced by each participating GSK Country Medical Department with the appropriate text upon receipt of the protocol and before they distribute it further within their country.

## TITLE PAGE

**Division:** Worldwide Development  
**Information Type:** Clinical Protocol

<b>Title:</b>	A long term, randomised, double blind, placebo-controlled study to determine the effect of albiglutide, when added to standard blood glucose lowering therapies, on major cardiovascular events in patients with Type 2 diabetes mellitus  Harmony Outcomes Trial
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**Subject:** Type 2 diabetes, albiglutide, cardiovascular outcomes, cardiovascular risk, safety.

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**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

I confirm agreement to conduct the study in compliance with the protocol.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

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Investigator Signature

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## LIST OF ABBREVIATIONS

ACCF	American College of Cardiology Foundation
ADA	American Diabetes Association
AE	adverse event
AHA	American Heart Association
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANCOVA	analysis of covariance
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BI	baseline basal insulin population
BMI	body mass index
bpm	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEC	Cardiovascular Endpoint Committee
CI	confidence interval
CPK	creatine phosphokinase
CONSORT	Consolidated Standards of Reporting Trials
DCRI	Duke Clinical Research Institute
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EHR	electronic health record
ESC	European Society of Cardiology
FDA	US Food and Drug Administration
FRP	females of reproductive potential
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GSK	GlaxoSmithKline
HbA1c	glycated haemoglobin
hCG	human chorionic gonadotrophin
HLA	human leukocyte antigen
HRT	hormone replacement therapy
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normal range
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	Interactive Voice Response System
KM	Kaplan-Meier

LDH	lactate dehydrogenase
LFT	liver function test
MACE	major adverse cardiovascular event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MSDS	Material Safety Data Sheet
MTC	medullary thyroid cancer
NHLBI	National Heart, Lung and Blood Institute
NI	non-insulin population
PAD	peripheral arterial disease
PD	pharmacodynamics
PHI	Protected Health Information
PK	pharmacokinetics
PP	per protocol
RAP	Reporting Analysis Plan
RR	relative risk
s.c.	subcutaneous
SAE	serious adverse event
SRM	Study Reference Manual
SU	sulfonylureas
TIA	transient ischemic attack
TRIM-D	Treatment Related Impact Measures-D
ULN	upper limit of normal range
WHF	World Heart Federation
WHO	World Health Organization

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## PROTOCOL SUMMARY

### Rationale

Albiglutide is a novel analogue of glucagon-like peptide-1 (GLP-1) with a sufficiently long half-life to permit once a week injection. Albiglutide is licensed for the treatment of type 2 diabetes as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies, including basal insulin. The Food and Drug Administration (FDA) has issued guidance on evaluating cardiovascular risk in new anti-diabetic therapies to treat type 2 diabetes [FDA [Guidance for Industry](#), 2008]. For a premarketing application that contains a meta-analysis of major adverse cardiovascular events (MACE) for which the upper bound of the 95 percent confidence interval for the relative risk is between 1.3 and 1.8, a post-marketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. The MACE meta-analysis of the albiglutide Phase III program (primary endpoint cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina), whilst ruling out an upper bound of the confidence interval for cardiovascular events of 1.8, was not able to rule out (due to a relatively small number of events) a relative risk (RR) upper bound of 1.3. For this reason GlaxoSmithKline (GSK) will conduct this cardiovascular outcome study as a US post-marketing requirement, to evaluate the effect of albiglutide on cardiovascular events in subjects with type 2 diabetes.

### Objectives/Endpoints

Objectives	Endpoints
<b>Primary</b>	
To determine whether albiglutide is non-inferior with respect to MACE when added to glycaemic standard of care versus standard of care alone	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke) [Non-inferiority]</li> </ul>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE [Superiority]<sup>(1 see footnote)</sup></li> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start. <sup>(1 see footnote)</sup></li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li>The proportion of subjects achieving glycaemic control (HbA1c ≤ 7.0% at final assessment) with no severe hypoglycaemic incidents and weight gain &lt;5% of body weight. <sup>(1 see footnote)</sup></li> <li>The time to first occurrence of a clinically important microvascular event (see Section <a href="#">6.2.4</a>)</li> <li>Change in glycated haemoglobin (HbA1c)</li> </ul>

Objectives	Endpoints
	<ul style="list-style-type: none"> <li>Change in body weight</li> <li>Patient reported outcomes from Treatment Related Impact Measures-D (TRIM-D)/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>All cause mortality</li> <li>Non-fatal serious adverse events (SAEs)</li> <li>Adverse events (AEs) leading to discontinuation of investigational product</li> <li>AE of special interest (see Section 6.2.3)</li> <li>Change in estimated glomerular filtration rate (eGFR) calculated using Modification of Diet in Renal Disease (MDRD) formula</li> <li>Change in blood pressure and heart rate</li> </ul>

1. If the primary endpoint meets the criteria for non-inferiority, a multiple comparisons adjustment strategy will be performed for these 3 secondary endpoints as specified in the Section 8.3.5.

## Overall Design

This is a randomised, double blind, parallel group, placebo-controlled study.

## Treatment Arms and Duration

All subjects will receive standard of care for their diabetes and cardiovascular health which can be adjusted by the healthcare professional responsible for the subject during the study according to clinical need and with close adherence to professional society treatment guidelines. The study comparison is thus between albiglutide added to standard of care and standard of care alone. Placebo injections will be used to ensure study assessments are performed without knowledge of treatment assignment. Treatment with albiglutide or placebo will be randomly allocated in a 1:1 ratio. The starting dose of albiglutide is 30 mg weekly which may be up-titrated to 50mg weekly if further improvement of glycaemic control is required.

The study will be event driven, i.e. follow up will continue until it is projected that approximately 611 adjudicated MACE events will have occurred. Consequently, the maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate, and is estimated to be between 3 and 5 years.

An Independent Data Monitoring Committee (IDMC) will have study oversight to ensure participant safety and scientific integrity of the data.

## Type and Number of Subjects

A total of 9400 subjects with type 2 diabetes and a previous history of cardiovascular disease and who do not have optimal glycaemic control will be studied.

## Analysis

The study's primary question is whether albiglutide is non-inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. The primary analysis is an Intent-to-Treat (ITT) analysis of the time to the first occurrence of MACE using Cox's Proportional Hazard regression.



## 1. INTRODUCTION

### 1.1. Background

Diabetes affects an estimated 347 million people worldwide, with type 2 diabetes accounting for more than 90% of cases [WHO, 2013]. The primary manifestation of this disease is chronic hyperglycaemia, resulting from resistance to insulin action at a cellular and molecular level and a relative inadequacy in the secretion of endogenous insulin [American Diabetes Association, 2014]. Chronic hyperglycaemia has been firmly established as a key factor in the development of microvascular complications (retinopathy, nephropathy, and neuropathy). Individuals with type 2 diabetes are also at greatly elevated risk of cardiovascular disease.

The management of glycaemia in individuals with type 2 diabetes consists of diet, exercise, and weight reduction together with oral anti-diabetic drug, injectable agents such as GLP-1 receptor agonists or insulin therapy, to achieve near normoglycaemia as reflected by a target HbA1c level of  $\leq 7\%$ , where possible, without significant hypoglycaemia or other adverse effects of treatment. Despite the large number of available therapeutic agents, a high proportion of subjects fail to achieve or maintain target HbA1c levels [Khunti, 2013] owing to the inexorable decline in endogenous insulin production characteristic of the disease, and limitations in existing treatments. New agents with complementary mechanisms (permitting combination use) or more favourable safety profiles are needed to help more subjects achieve glycaemic targets.

GLP-1 is secreted by intestinal L-cells in response to ingestion of food. In a healthy individual, it plays an important role regulating postprandial blood glucose by stimulating glucose-dependent insulin secretion by the pancreas. GLP-1 suppresses glucagon secretion, leading to reduced hepatic glucose output. It also delays gastric emptying time and slows small bowel motility, delaying food absorption and slowing the rate of glucose appearance in the blood. In patients with type 2 diabetes the postprandial rise in endogenous GLP-1 is absent or reduced [Vilsbøll, 2001].

GLP-1 receptor agonists have been developed as anti-hyperglycemic therapy for type 2 diabetes to replace or supplement endogenous GLP-1 in order to increase meal-related insulin secretion, reduce inappropriate glucagon secretion, and slow GI motility. They have demonstrated substantial effectiveness in improving glycaemic control while mitigating the risk of hypoglycaemia and weight gain commonly associated with some of the other treatments for type 2 diabetes [Stonehouse, 2012].

Albiglutide is a novel analogue of GLP-1 generated through a genetic fusion of 2 modified recombinant human GLP-1 molecules linked in tandem to recombinant human albumin. Albiglutide is licensed for the treatment of type 2 diabetes as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies (oral anti-diabetic therapies or basal insulin). It has been granted marketing authorisation by the European Medicines Agency (EMA) (March 2014) and the FDA (April 2014). Details of the clinical trial results can be found in the Investigator Brochure (IB).

## 1.2. Rationale

The FDA has issued guidance on evaluating cardiovascular risk in new anti-diabetic therapies to treat type 2 diabetes [FDA [Guidance for Industry](#), 2008]. For a premarketing application that contains a meta-analysis of MACE, for which the upper bound of the 95 percent confidence interval for the relative risk is between 1.3 and 1.8, a post-marketing trial may be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3.

The MACE + meta-analysis of the albiglutide Phase III program (primary endpoint cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina), whilst ruling out an upper bound of the confidence interval for cardiovascular events of 1.8, was not able to rule out (due to a relatively small number of events) a RR upper bound of 1.3. For this reason GSK will conduct this cardiovascular outcome study as a US post-marketing requirement, to evaluate the effect of albiglutide on cardiovascular events in subjects with type 2 diabetes.

Preclinical studies have provided evidence that GLP-1 receptor stimulation favourably effects endothelial function, recovery from ischemic injury, and myocardial function in animals [reviewed in [Okerson](#), 2012]. Albiglutide reduced infarct size assessed 24 hours after 30 minutes temporary left anterior descending coronary artery occlusion in normoglycaemic rats [[Bao](#), 2011]. GLP-1 infusion has been shown to improve endothelial function in subjects with stable coronary disease [[Nystrom](#), 2004]. In subjects with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, the GLP-1 receptor agonist, exenatide, administered at the time of reperfusion has been reported to increase myocardial salvage [[Lønborg](#), 2012]. In the Phase III studies, small mean increases in heart rate (1 to 2 bpm) and a higher incidence of atrial fibrillation/flutter events were observed with albiglutide. It is difficult to predict whether these preclinical and clinical findings will translate into effect on major cardiovascular events.

## 2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b>	
To determine whether albiglutide is non-inferior with respect to MACE when added to glycaemic standard of care versus standard of care alone	<ul style="list-style-type: none"> <li>Time to first occurrence of MACE (cardiovascular death, myocardial infarction, or stroke) [Non-inferiority]</li> </ul>
<b>Secondary</b>	
To supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes	<ul style="list-style-type: none"> <li><b>Time to first occurrence of MACE [Superiority]</b><sup>(1 see footnote)</sup></li> <li>Time to first occurrence of the following: <ul style="list-style-type: none"> <li>MACE or urgent revascularisation for unstable angina</li> <li>The individual components of the primary endpoint</li> <li>Cardiovascular death or hospitalization due to heart failure</li> </ul> </li> </ul>
To evaluate the effects of albiglutide on metabolic management of type 2 diabetes	<ul style="list-style-type: none"> <li><b>Time to initiation of insulin of more than 3 months duration for those subjects not treated with insulin at study start</b> <sup>(1 see footnote)</sup></li> <li>Time to initiation of prandial insulin in those subjects on basal insulin at study start</li> <li><b>The proportion of subjects achieving glycaemic control (HbA1c ≤ 7.0% at final assessment) with no severe hypoglycaemic incidents and weight gain &lt;5% of body weight</b> <sup>(1 see footnote)</sup></li> <li>The time to first occurrence of a clinically important microvascular event (see Section 6.2.4)</li> <li>Change in HbA1c</li> <li>Change in body weight</li> <li>Patient reported outcomes from TRIM-D/EQ5D</li> </ul>
To evaluate the safety of albiglutide	<ul style="list-style-type: none"> <li>All cause mortality</li> <li>Non-fatal SAEs</li> <li>AEs leading to discontinuation of investigational product</li> <li>AE of special interest (see Section 6.2.3)</li> <li>Change in eGFR calculated using MDRD formula</li> <li>Change in blood pressure and heart rate</li> </ul>
<b>Exploratory</b>	
To evaluate patient reported experience of diabetes treatment	<ul style="list-style-type: none"> <li>Patient reported outcomes from study specific questionnaire</li> </ul>
To evaluate (at a subset of sites) barriers to using the electronic health record (EHR) to facilitate trial enrolment and the quality of EHR data for use in populating baseline characteristics and identifying events of interest during trial follow-up. <sup>2</sup>	<ul style="list-style-type: none"> <li>Workflow impact of an EHR-generated list of subjects to facilitate trial enrolment.</li> <li>Concordance, sensitivity, specificity, and accuracy of baseline characteristics extracted from the EHR compared with those reported on the electronic case report form (eCRF)<sup>3</sup></li> <li>Concordance, sensitivity, specificity, and accuracy of EHR-identified events compared with study events <sup>3,4</sup></li> <li></li> </ul>

1. If the primary endpoint meets the criteria for non-inferiority, a multiple comparisons adjustment strategy will be performed for these 3 secondary endpoints as specified in the Section 8.3.5.
2. Details are provided in a separate EHR ancillary study protocol (Appendix 7). Results from this exploratory investigation will be reported separately from the main clinical study report.
3. Comparison of EHR identified events with study events will be conducted in the same data subset.
4. Analyses to be undertaken after the main trial results are published.

### 3. STUDY DESIGN

#### 3.1. Overall Design

This is a Phase IV, randomised, double blind, parallel-group, placebo-controlled, multicentre study. This study will recruit approximately 9400 subjects with type 2 diabetes and a previous history of cardiovascular disease who are failing to achieve optimal glycaemic control on their current anti-hyperglycaemic regimen. Subjects will be randomised in a 1:1 ratio to albiglutide or albiglutide matching placebo administered once weekly by subcutaneous (s.c.) injection.

All subjects will receive standard of care which can be adjusted by their usual care provider(s) during the study according to clinical need (See Section 3.2). The study comparison is between albiglutide added to standard of care and standard of care alone.

The starting dose of albiglutide will be 30 mg once weekly. If at any stage after 5 weeks of treatment the subject needs to have intensified therapy to improve glycaemic control, the dose of investigational product should be increased before altering the doses of or adding other glucose-lowering medication. This treatment decision will be the responsibility of the investigator. In this case the subject will be called in for an unscheduled visit to increase the dose from 30 mg to 50mg. Subjects randomly assigned to albiglutide matching placebo will also go through the increased dose procedure to maintain study blind. If a subject experiences tolerability issues with the higher, 50mg dose then the investigator may decrease the dose back to 30 mg without the need for an unscheduled visit to supervise down titration. Use of GLP-1 receptor agonists will be prohibited but other glucose-lowering medications permitted, provided they are not contraindicated for the individual subject concerned.

This study is designed with minimal intervention above normal clinical care of subjects with type 2 diabetes, whilst allowing thorough evaluation of cardiovascular and other events of special interest (Section 6.2.3), thus investigating the safety of albiglutide in the typical clinical situation. Sites will employ pre-screening to assess potential subjects for study entry. Screening and randomisation can then occur at the same visit or in close proximity depending on scheduling. Contact with subjects will be every four months after the randomisation visit. HbA1c will be measured at 4 month clinic visits. Serum creatinine and liver function tests (LFTs) will be measured and a targeted physical assessment performed at 8 month clinic visits (Table 1).

The study will be event driven, i.e., follow up will continue until it is projected that approximately 611 adjudicated MACE events will have occurred. Consequently, the maximum duration of the study for an individual participant is dependent both on the time taken for recruitment and the MACE event rate, and is estimated to be between 3 and 5 years. If the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years, respectively.

An Executive Committee will be the main decision-making body for the study, in collaboration with the Sponsor (GSK). It is charged with the overall scientific, professional and operational conduct of the study. Amongst other roles pre-specified in

its Charter, the Executive Committee will ensure proper study conduct and conformance to the protocol, consider and agree changes to the protocol based on emerging scientific and/or clinical advances (e.g., new emerging data with other GLP-1 receptor agonists), advise on the selection of study sites and assist in subject recruitment strategies.

An IDMC will have study oversight to ensure participant safety and scientific integrity of the data (Section 9.8), an independent Cardiovascular Endpoint Committee (CEC) blinded to treatment allocation will adjudicate cardiovascular outcome events (Section 6.2.1) and a Pancreatitis Adjudication Committee will adjudicate potential events of pancreatitis.

Subject completion is defined as completion of all periods of the study up to and including any follow-up period.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 1), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

### **3.2. Standard of Care**

Anti-hyperglycaemic and cardiovascular medications will be used at the discretion of the usual care provider(s) (or investigator if also the usual care provider), who will be informed of the patient's enrolment in the trial, the use of blinded trial medication, and that use of GLP-1 receptor agonists (other than the use of randomised albiglutide) is contraindicated during the trial period. Usual care providers will be encouraged to follow the most up to date guidelines for diabetes and cardiovascular care based upon local and institutional practice patterns and any relevant published practice guidelines (e.g., Inzucchi, 2012). Treatment for type 2 diabetes will be captured by name and total daily dose at the time of study visits, while other relevant (cardiovascular) concomitant medications will be collected only as drug classes (see Section 5.6.1).

During the study investigators are expected to monitor patients' type 2 diabetes regimens and communicate with usual care providers, who will be responsible for adjusting their regimen in order to achieve locally-appropriate HbA1c goals. The Executive Committee and National Country Leaders will encourage investigators to follow clinical care practice guidelines published by national and international societies regarding type 2 diabetes over the course of the trial. These practice guideline goals will be individualized, with the understanding that currently applicable glycaemic guidelines may vary among different geographic regions. With adherence to local custom and laws (including privacy regulations such as the Health Insurance Portability and Accountability Act), types of communication may be informal e.g. email or telephone exchanges, to enhance frequency and ease of two-way communication.

Any agent, with the exception of GLP-1 receptor agonists, is acceptable for reaching HbA1c goals. If HbA1c goals are not met following adjustment with oral medications in patients not receiving insulin, an insulin regimen may be initiated. Patients already receiving insulin therapy may up-titrate insulin during the trial if necessary. Patients should be reminded to keep taking their blinded trial medication throughout the course of the trial even in the case after initiation of insulin.

The Executive Committee and National Country Leaders will also monitor the standard of care of management of diabetes and cardiovascular disease. Similar to the management of type 2 diabetes, sites and investigators will be expected to adhere to local clinical practice guidelines. Sites will be provided training on clinical management guidelines to re-enforce standard of care adherence. Information on medications important to management of cardiovascular risk will be captured during study visits. The Executive Committee and National Country Leaders will review on a periodic basis the use of medications for cardiovascular risk prevention to ensure patients are receiving standard of care. If there are unusually low goal attainments for standard of care, site investigators will be advised accordingly.

### **3.3. Discussion of Design**

This study is a clinical outcomes trial required by FDA as a post-marketing requirement to evaluate cardiovascular safety. It will provide important information regarding the cardiovascular safety and metabolic effects of albiglutide treatment of subjects with type 2 diabetes. Sufficient MACE events must be observed during the study to permit the assessment of cardiovascular safety. Consequently, to enter the study subjects must have established cardiovascular disease as well as type 2 diabetes. The study is powered on a predefined number of clinical events, consequently the number of subjects required and study duration may vary from that stated in the protocol.

This will be a double-blind, placebo-controlled study. All subjects will receive placebo or albiglutide in addition to usual standard of care for type 2 diabetes and cardiovascular disease, in order to assess the effect of albiglutide above that of currently available therapies alone.

The primary cardiovascular comparison will be to assess whether albiglutide is non-inferior to placebo with respect to time to first MACE. Missing data may inappropriately bias comparison towards declaring non-inferiority. The longer the duration of a study, the more difficult it is to avoid loss to follow-up and other sources of missing data. The product of the projected duration of this study and the number of subjects to be studied is intended to minimize the risk of missing data whilst still permitting the assessment of the safety of albiglutide to be over an appreciable period of time. Every effort will be made to keep subjects on their assigned study medication according to the protocol. Subjects who stop study medication will be followed throughout the whole study duration. More details about procedures for subject follow-up are provided in Section 4.5.

Phase III studies confirmed the glycaemic efficacy of both 30 mg and 50 mg doses of albiglutide, and both were generally well-tolerated. Although the 30 mg dose was effective at controlling glycaemia for at least 2 years in many subjects with type 2

diabetes, an increase in dose to 50 mg weekly offered additional benefit without significant safety issues (See IB for further details).

### **3.4. Benefit:Risk Assessment**

Albiglutide has been evaluated in an international programme of studies involving approximately 9000 subject-years of overall exposure to date (including over 4000 subject-years of exposure to albiglutide). The programme included 8 well-controlled Phase III studies (including one in subjects with concurrent renal impairment), ranging in duration from 32 weeks to 3 years, and using both 30 mg and 50 mg once weekly dosing. This has permitted a thorough assessment of efficacy, safety, and tolerability in a population of subjects with type 2 diabetes that spanned newly diagnosed individuals treated with diet and exercise alone through to subjects on background oral monotherapy, oral dual therapy, oral triple therapy, and basal insulin.

Summaries of findings from both clinical and non-clinical studies conducted with albiglutide can be found in the IB and in the product labelling for those countries where marketing authorisation has been granted. The following section outlines the risk assessment and mitigation strategy for this protocol:

#### **3.4.1. Risk Assessment**

The identified and potential risks associated with the use of albiglutide, or the GLP-1 receptor agonist class, as well as the mitigation strategy for key risks of clinical significance are provided below. Please refer to the IB for a thorough summary of the nonclinical and clinical experience with albiglutide as well as the complete Guidance for the Investigator. The risks associated with study comparator, placebo, are also provided below. Subjects will have the AE profile of GLP-1 receptor agonists, and albiglutide in particular, explained to them by the investigator and via the informed consent form.

##### **3.4.1.1. Identified Risks**

**Pancreatitis.** Acute pancreatitis has been reported in association with albiglutide and other GLP-1 receptor agonists in clinical trials and during postmarketing experience. Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether they are at increased risk for pancreatitis. Subjects with a history of pancreatitis or who are considered at significant risk of developing pancreatitis are excluded from entering the study. Subjects will be informed of the characteristic symptom of pancreatitis: persistent severe abdominal pain. If pancreatitis is suspected, investigational product should be promptly discontinued and if pancreatitis is confirmed, investigational product will not be restarted.

**Gastrointestinal events.** Albiglutide has not been studied in subjects with severe gastrointestinal (GI) disease, including severe gastroparesis. Subjects with severe gastroparesis will be excluded from the study. Use of albiglutide and other GLP-1 receptor agonists can be associated with GI side effects such as diarrhoea, nausea, and vomiting; the frequency of these events increased as renal function decreased. These types of GI reactions can be associated with dehydration and worsened renal function.



(see below and see Section 4.4.4). Other GI related adverse reactions with albiglutide include dyspepsia, gastro-oesophageal reflux disease and constipation.

**Hypoglycaemia.** Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycaemia. However, when used in combination with insulin (or insulin secretagogues) the risk of hypoglycaemia is increased. Investigators will be reminded that it may be necessary to reduce the dose of insulin or insulin secretagogues when starting study medication to reduce the risk of hypoglycaemia. Routine standard of care for subjects treated with insulin secretagogues and insulin includes advice about avoidance of hypoglycaemia which will be reinforced. All subjects are required to have a last indicator of glycemic control of above HbA1c = 7% which is expected to reduce the risk of hypoglycaemia when starting albiglutide.

**Immunogenicity.** Hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III programme. In the Phase III programme one subject (anti-albiglutide antibody negative) developed rash, itching and dyspnoea. Subjects with known allergy to any GLP-1 receptor agonist or excipients of albiglutide are excluded from the study. Subjects will be informed of the symptoms of severe hypersensitivity or allergy and be advised to seek medical assistance immediately. In the Phase III programme approximately 5% of subjects developed anti-albiglutide antibodies. Subjects who tested positive for anti-albiglutide antibodies experienced a similar glycaemic response (HbA1c and fasting plasma glucose) to those who did not test positive for antibodies. Other than injection site reactions (see below), the overall safety profile appeared similar among the subset of subjects who did and those who did not test positive for anti-albiglutide antibodies. Anti-albiglutide antibody formation is not expected to impact the overall safety of albiglutide treatment and therefore will not be measure routinely in this study.

**Injection site reactions.** Albiglutide injections may cause rash, erythema or itching and/or other reactions at the site of injection. Subjects will be advised that when injecting in the same region, to use a different injection site each week. In the Phase III program, most subjects with injection site reactions did not test positive for anti-albiglutide antibodies. However, injection site reactions were reported more frequently among those who did test positive for anti-albiglutide antibodies (41% of the antidrug antibody positive subjects reported one or more injection site reactions) than among those who were consistently antibody negative (14% of the antidrug antibody negative subjects reported one or more injection site reactions).

**Other adverse reactions** (e.g. pneumonia, atrial fibrillation/flutter, and appendicitis). In the Phase III programme in type 2 diabetes, other possible albiglutide related adverse reactions were identified. These events occurred at a cumulative incidence <3% in studies up to 3 years in duration. These events were reported more frequently with albiglutide than comparators.

#### 3.4.1.2. Potential Risks

**Thyroid C-cell tumours.** GLP-1 receptor agonists, including albiglutide increase serum calcitonin in rodents and other GLP-1 receptor agonists are associated with thyroid C-cell focal hyperplasia and C-cell tumours in rodents. It is unknown whether GLP-1 receptor



agonists are associated with thyroid C-cell tumours in humans, including medullary thyroid cancer (MTC). Subjects with a personal or family history of MTC or subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) are excluded from the study. Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. Routine monitoring of serum calcitonin is not recommended. However, if serum calcitonin is found to be elevated the subject should be referred to a specialist for further evaluation. If MTC or other thyroid C-cell neoplasia is diagnosed, investigational product will be discontinued.

**Other malignant neoplasms** Concerns have been raised regarding use of incretin based therapies and other malignancies such as pancreatic cancer [Egan, 2014], malignancy when used in combination with insulin based on hypotheses of biological plausibility [European Public Assessment Report, 2014], and haematological malignancies [FDA Summary Basis of Approval, 2014].

**Hepatotoxicity.** Hepatotoxicity is an area of interest in drug development. Patients with type 2 diabetes are at increased risk for liver enzyme abnormalities and disease related liver conditions. One subject treated with albiglutide in the Phase III clinical programme developed probable drug induced liver injury with an asymptomatic elevation in alanine amino transferase (ALT) and total bilirubin although the cases had some atypical features and complicating factors. Routine liver safety laboratory evaluations will be conducted and specific withdrawal criteria for elevated liver function tests have been defined (See Section 4.4.3).

**Subject population with severe renal impairment (eGFR <30 mL/min/1.73m<sup>2</sup>).** Experience in type 2 diabetes subjects with severe renal impairment is limited (in the Phase III programme a total of 19 subjects with eGFR <30 mL/min/1.73m<sup>2</sup> received albiglutide).

In a Phase 3 study of patients with varying degrees of renal impairment, in the albiglutide group, on-therapy GI AEs occurred with a higher incidence and higher event rate in subjects with moderate and severe renal impairment compared to those with mild renal impairment. Because these GI events may lead to dehydration and worsen renal function, worsening renal function will be closely evaluated as an AE of special interest, serum creatinine will be measured every 8 months, and subjects will discontinue IP if eGFR falls below 15 mL/min/1.73m<sup>2</sup>. Subjects with known severe renal impairment are excluded from the study (see Section 4.4.4).

**Drug Interactions.** Like other members of the class, albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the development programme, drug interactions studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant PK or PD effects. Investigators will be advised to take the effect of albiglutide on gastric emptying into account when prescribing concomitant medication.

**Pregnancy and Lactation.** Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. It is not known if albiglutide is secreted into human milk during lactation. Given that albiglutide is an albumin-based protein

therapeutic, it is likely to be present in human milk. Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation. Subjects who are breastfeeding, pregnant or planning a pregnancy during the course of the study are excluded. Additionally, all females of child-bearing potential must be taking adequate contraception during the study and have a negative pregnancy test prior to entry.

**Placebo control.** In subjects treated with placebo, symptoms and long-term risks of hyperglycaemia may not improve or may worsen. During the study, intensification of glucose-lowering treatments other than study drug will be allowed in both treatment arms with a treat-to-target approach. Albiglutide placebo injections may cause injection site reactions. Subjects will be advised when injecting into the same region to use a different injection site each week.

### **3.4.2. Benefit Assessment**

In subjects with type 2 diabetes albiglutide treatment resulted in clinically relevant lowering of HbA1c at both the 30 mg and 50 mg doses when given as monotherapy and in combination with metformin, sulfonylureas (SUs), thiazolidinedione or basal insulin . The durability of the effect on glycaemic control was shown over a study period of up to 3 years. Consistent with its mechanism of action, albiglutide was not associated with clinically relevant hypoglycaemia except when used in combination with an SU or insulin, and incidence rates with the combination were less than those reported with SUs or insulin alone. Treatment with albiglutide generally produced a steady reduction in weight over time.

For subjects not yet on insulin at the start of the study, data from the Phase III programme suggest that the use of albiglutide once weekly in a pen device may have the potential to delay the need to start daily insulin injections. This will be formally assessed within this trial. Similarly, it is possible that for those already taking basal insulin, albiglutide may delay the need to introduce short-acting prandial injections and for those taking basal/bolus or pre-mixed insulin, it may reduce the dosage of insulin and/or the number of daily injections needed to achieve good glycaemic control. These will also be evaluated in the study.

Subjects in the placebo arm will also be receiving effective anti-hyperglycaemic medication which will be titrated up or down as required to improve or maintain glycaemic control, and therefore these subjects should also demonstrate reductions in HbA1c, though weight gain (rather than weight loss) may occur depending upon the medication selected.

Finally, as a result of participating in a clinical trial, each subject will receive more contact with the study site than would be performed as part of their usual standard of care.

### **3.4.3. Overall Benefit:Risk Conclusion**

Taking into account the measures taken to minimise risk to subjects participating in this study, the known and potential risks identified with albiglutide are justified by the benefits have been demonstrated in subjects with type 2 diabetes.

## **4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA**

### **4.1. Inclusion Criteria**

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB for albiglutide and in the product label for those countries where marketing authorisation has been granted.

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

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

1. Men or women at least 40 years old with a diagnosis of type 2 diabetes.
2. Established cardiovascular disease, including at least 1 of the following:
  - a. Coronary artery disease with EITHER of the following:
    - Documented history of spontaneous myocardial infarction, at least 30 days prior to Screening.
    - Documented coronary artery disease (CAD)  $\geq 50\%$  stenosis in 1 or more major epicardial coronary arteries, determined by invasive angiography, or history of surgical or percutaneous (balloon and/or stent) coronary revascularization procedure (at least 30 days prior to Screening for percutaneous procedures and at least 5 years prior to Screening for coronary artery bypass graft (CABG)).
  - b. Cerebrovascular disease – ANY of the following:
    - Documented history of ischaemic stroke, at least 90 days prior to study entry.
    - Carotid arterial disease with  $\geq 50\%$  stenosis documented by carotid ultrasound, magnetic resonance imaging or angiography, with or without symptoms of neurologic deficit.
    - Carotid vascular procedure (e.g. stenting or surgical revascularisation), at least 30 days prior to Screening.
  - c. Peripheral arterial disease (PAD) with EITHER of the following:
    - intermittent claudication and ankle:brachial index  $< 0.9$  in at least one ankle
    - prior non-traumatic amputation, or peripheral vascular procedure (e.g. stenting or surgical revascularisation), due to peripheral arterial ischaemia.

3. HbA1c >7.0% (53 mmol/mol) based on the most recent documented laboratory assessment measured no more than 6 months prior to randomization. Local laboratory HbA1c values taken as part of usual care are permitted.
4. Female: subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test for females of reproductive potential only), not breastfeeding, and at least one of the following conditions applies:
  - a) Reproductive potential and agrees to follow one of the options listed in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (e.g, combined oral contraceptive pill; see [Appendix 2](#)) from 30 days prior to the first dose of study medication and until after the last dose of study medication and completion of the follow-up visit.

This does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent. Other situations in which contraception in FRP may not need to be mandated should be discussed with the Medical Monitor.
  - b) Non-reproductive potential defined as either:
    - Pre-menopausal with one of the following: (i) documented tubal ligation; (ii) documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion; (iii) hysterectomy; or (iv) documented bilateral oophorectomy, or;
    - Postmenopausal defined as 12 months of spontaneous amenorrhea and age appropriate (i.e. >50 years). In questionable cases, a blood sample with simultaneous follicle stimulating hormone (FSH) >40 mIU/mL and oestradiol <40 pg/mL (<140 pmol/L) is confirmatory, depending on local laboratory ranges. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.
5. Able and willing to provide informed consent.

## 4.2. Exclusion Criteria

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

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

1. eGFR calculated using MDRD formula <30mL/min/1.73m<sup>2</sup> (based on the most recent documented serum creatinine laboratory assessment measured no more than 6

months prior to randomization. Local laboratory creatinine values taken as part of usual care are permitted) or renal replacement therapy.

2. Use of a GLP-1 receptor agonist at Screening.
3. Severe gastroparesis requiring therapy within 6 months prior to Screening.
4. History of pancreatitis or considered clinically at significant risk of developing pancreatitis during the course of the study (e.g. due to symptomatic gallstones, excess alcohol use).
5. Personal or family history of medullary carcinoma of the thyroid or subject with MEN-2. Personal history of pancreatic neuroendocrine tumours. In the opinion of the investigator, the subject has a medical history which might affect his / her ability to remain in the study for its entire duration, or which might limit management, such as life expectancy of <5 years (e.g. due to active malignancy).
6. Subject has a medical history which in the opinion of the investigator might limit the individual's ability to take trial treatments for the duration of the study or to otherwise complete the study.
7. Breastfeeding, pregnancy, or planning a pregnancy during the course of the study. Pregnancy test will be required in women of child bearing potential. Women who have undergone a sterilisation procedure or who are clearly post-menopausal will not be required to undergo pregnancy testing. Women who have developed spontaneous secondary amenorrhoea of 12 months or more where post-menopausal status is in doubt, a blood sample where FSH >40MU/ml and oestradiol <40 pg/mL (<14 pmol/L) are simultaneously measured will be considered confirmatory.
8. Known allergy to any GLP-1 receptor agonist or excipients of albiglutide.
9. Use of another investigational product within 30 days or according to local regulations, or currently enrolled in a study of an investigational device.
10. Any other reason the investigator deems the subject to be unsuitable for the study.

#### **4.3. Screening/Baseline Failures**

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements [Schulz, 2010], and respond to queries from regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any SAEs.

Re-screening of subjects who did not meet the eligibility criteria for HbA1c or creatinine based on local laboratory values taken as part of usual care is permitted. If values were based on laboratory results as part of usual care then one re-test is permitted within the

protocol at Screening. Any future re-screening will be based on laboratory results obtained as part of usual care.

#### **4.4. Criteria for Early Discontinuation of Investigational Product**

The primary analysis will be conducted on an ITT analysis basis so it is important that every subject is followed for the duration of the study, regardless of whether the subject continues to take investigational product, unless consent for all follow up is actively withdrawn.

The requirements for handling early discontinuations from investigational product are described below. Details of the requirements for subject follow-up are provided in Section 4.5.

##### **4.4.1. Early Discontinuation of Investigational Product**

If a subject chooses to discontinue investigational product between scheduled face-to-face visits they should be encouraged to contact the investigator site by telephone. Subjects should first be counselled to consider temporary discontinuation of investigational product prior to choosing to discontinue investigational product permanently, unless the reason for discontinuation is one of those listed below (Reasons for Discontinuation of Investigational Product). If the discontinuation is permanent, the subject should be asked to attend the clinic as soon as possible to complete the assessments as for the final study visit (see Table 1) and then continue in the study for follow-up. The procedures for follow-up for a subject who permanently discontinues treatment with investigational product prior to the study end are given in Section 4.5.

In all cases, reasons for discontinuation of investigational product and the date of last dose will be recorded.

##### **4.4.2. Reasons for Discontinuation of Investigational Product**

Any subject experiencing the following will be required to discontinue investigational product:

- AE:
  - Pancreatitis, acute or chronic.
  - Pancreatic cancer.
  - MTC or other thyroid C-cell neoplasia. In subjects where a treatment emergent thyroid nodule is identified, if serum calcitonin is measured at the discretion of the Investigator (e.g., per local guidelines) and found to be >100 ng/L this should prompt further investigation for MTC and potential interruption or discontinuation of investigational product until diagnosis has been resolved.
  - Liver chemistry abnormalities exceeding the threshold criteria outlined in Section 4.4.3
  - Severe allergic/hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology.

- Other AE which, in the opinion of the investigator precludes continuation of dosing.
- eGFR<15ml/min/1.73m<sup>2</sup> (Section 4.4.4) or the need for renal replacement therapy.
- Subject becomes pregnant during the study.
- Need for chronic use of a prohibited concomitant medication (Section 5.6.2)
- Decision by subject or proxy.
- Sponsor terminated study.
- Investigator site closed and subject was unable to transfer to another investigative site.

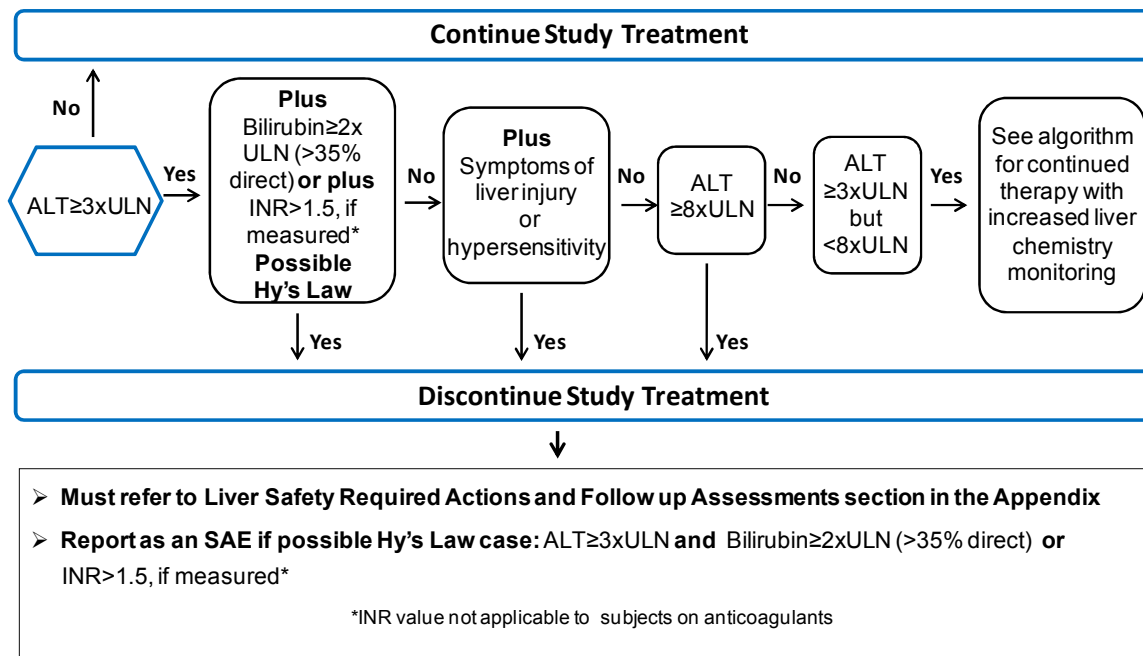
If investigational product is discontinued, the subject should continue in the study and be followed until the final study visit as detailed in Section 4.5.

#### 4.4.3. Liver Chemistry Stopping Criteria

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

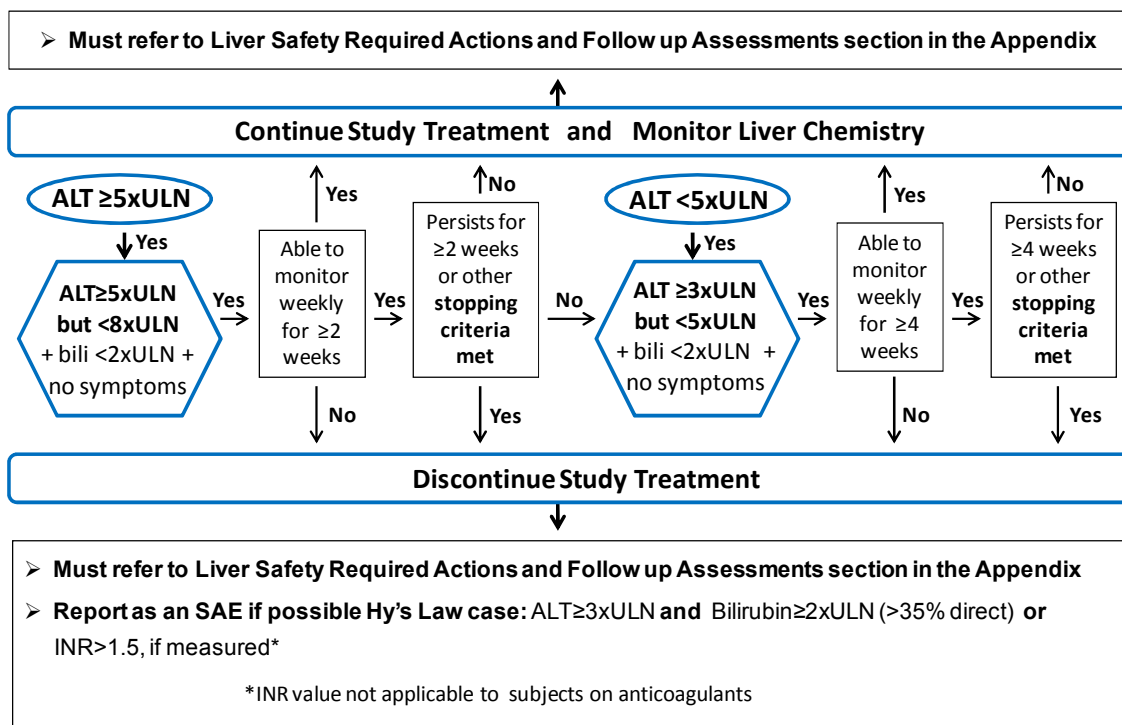
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

#### Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver safety required actions and follow up assessments section can be found in [Appendix 3](#).

### Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3 \times \text{ULN}$ but $< 8 \times \text{ULN}$



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 3](#).

Drug re-challenge following drug induced liver injury is not allowed.

Restart may be considered if GSK Medical Governance approval is granted (see [Appendix 4](#) for details). Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with human leukocyte antigen (HLA) markers of liver injury.

#### 4.4.4. eGFR Stopping Criteria

A baseline eGFR  $\geq 30 \text{ mL/min/1.73m}^2$  is a requirement for entering the study. Subjects can continue to take investigational product if functioning well as long as eGFR is  $\geq 15 \text{ mL/min/1.73m}^2$ .

During this study, if a subject's eGFR approaches  $30 \text{ mL/min/1.73m}^2$  closer monitoring of renal function is considered prudent, according to standard clinical practice. Particular



care should be taken to monitor renal function in subjects with renal impairment reporting severe adverse GI events. If eGFR is  $<15\text{mL}/\text{min}/1.73\text{m}^2$  and considered irreversible based on consecutive measurements the investigational product should be discontinued, the subject continue in the study and be followed until the final study visit.

If eGFR is  $<15\text{mL}/\text{min}/1.73\text{m}^2$  and the patient is considered to have temporary acute kidney injury that is potentially reversible, the investigational product should be temporarily discontinued until the eGFR is stable and  $\geq 15\text{mL}/\text{min}/1.73\text{m}^2$ . Events considered to reflect worsening renal function should be reported as SAE/AEs and targeted eCRFs completed for this AE of special interest (Section 6.2.3).

#### **4.5. Procedures for Subject Follow-up**

As described in Section 4.4, subjects who permanently discontinue investigational product will be asked to attend the clinic as soon as possible. They will continue in the study for follow-up. They will be asked to return to clinic according to the 8 monthly visit schedule and in addition be contacted by telephone at a time corresponding to the 4-monthly visit they would have otherwise made to replenish study medication supply. If instead of these interim telephone contacts the subject prefers to attend clinic every 4 months as originally scheduled that is an acceptable alternative.

If a subject permanently discontinues investigational product and is unable to attend visits in-person, he/she will be contacted by telephone or other methods to assess study outcomes and vital status, unless the subject has specifically withdrawn consent for all forms of contact. Follow-up of subjects who withdraw consent for contact is described below.

Every effort should be made to educate the subjects on the importance of remaining in the study and attending scheduled study visits including those required after early discontinuation of investigational product.

Other subject follow-up options to collect study outcomes and vital status should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes and vital status is acceptable to the subject, then the subject will be deemed not to have withdrawn consent for follow-up.

##### **4.5.1. Withdrawal of Consent for Contact**

Subjects who no longer wish to attend study visits in-person will be asked to be contacted by telephone or other methods to assess study outcomes and vital status. However, if a subject specifically withdraws consent to be contacted for additional information, no further study visits or study-related telephone contacts can be conducted. Information regarding study outcomes or vital status will continue to be collected from available sources including those in the public domain. Additionally, alternative permitted options to obtain study outcomes and vital status will be reviewed based on accepted local laws and regulations. For any subject who withdraws consent for contact, the study site will be asked to document the discussion with the subject regarding each of the contact options that were offered.

#### **4.5.2. Subjects Deemed Lost to Follow-up**

Finally, investigators should make every effort to contact subjects who are deemed lost to follow-up and who have not withdrawn consent to follow-up contacts, including pursuing any alternative contact methods permitted by local regulations. Where permitted, a third party may be used to locate alternative subject contact information that will be provided to the investigator. All attempts to contact subjects will be documented in the subject's eCRF and source notes.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject. Should the subject continue to be unreachable, then and only then will he/she be considered "Lost to Follow-up". Nonetheless, efforts to attempt to locate and contact the subject will continue until the study end.

### **5. STUDY TREATMENTS**

#### **5.1. Investigational Product and Other Study Treatment**

Albiglutide (and albiglutide matching placebo) will be provided as a fixed-dose, fully disposable pen injector system for delivery of the investigational product (albiglutide or albiglutide matching placebo) from a prefilled dual chamber glass cartridge that is an integral part of the pen. The pen is intended for single use by the subject. It is designed for manual reconstitution of the dose, priming and insertion of the pen needle, and manual injection by the subject.

Albiglutide (or albiglutide matching placebo) is intended for self-administration as a subcutaneous injection in the abdomen, thigh or upper arm region. Rotation of use of injection sites is recommended. Albiglutide and insulin may be injected in the same body region but the injections should not be adjacent to each other. The albiglutide pen includes a mechanical locking system that prevents the user from manipulating the dose button before the cartridge has been fully reconstituted. Reconstitution is performed through rotation of the pen housing parts. The pen is designed to work with standard pen needles.

When the injector pen product is reconstituted by the subject, a neutral, isotonic solution is produced. Separate pens are required to deliver either 30 mg of albiglutide, 50 mg of albiglutide, or matching placebo in a 0.5-mL injection volume.

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

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS)

describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

The investigational product (albiglutide and albiglutide matching placebo) must be stored in a secure area at 2°C to 8°C and protected from freezing. Each site must maintain a temperature log. Access to and administration of the investigational product will be limited to the investigator and authorised site staff (investigator or designee). Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Procedures for the disposal of unused study treatment will be provided in the SRM.

Investigational product (albiglutide or albiglutide matching placebo) will be administered once weekly by subcutaneous injection. The first dose is to be administered at the clinic. The starting dose of albiglutide will be 30 mg once weekly. If at any stage after 5 weeks of treatment in the opinion of the investigator the subject needs to have intensified therapy to improve glycaemic control, the dose of investigational product should be increased before altering the doses of other glucose-lowering medication. In this case the subject will be called in for an unscheduled visit to supervise an increase in dose from 30 mg to 50 mg. Subjects randomly assigned to albiglutide matching placebo will also go through the increased dose procedure to maintain study blind. If a subject experiences tolerability issues with the higher, 50mg dose then the investigator may decrease the dose back to 30 mg without the need for an unscheduled visit to supervise down titration, other than for the subject to collect pens of the correct dose.

Albiglutide (or albiglutide matching placebo) may be administered at any time of day without regard to meals. Preferably, it should be administered once a week on the same day each week. The day of weekly administration can be changed if necessary as long as the last dose was administered 4 or more days previously. If a dose is missed, it should be administered as soon as possible within 3 days after the missed dose. Thereafter, subjects can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, subjects should wait and administer their next regularly scheduled weekly dose.

If a subject misses 4 or more consecutive doses, the investigator should contact the medical monitor to discuss options for helping assure better compliance.

## **5.2. Treatment Assignment**

Subjects will be assigned to study treatment in accordance with the randomisation schedule.

Randomised treatment assignment will be done via the Interactive Voice Response System (IVRS), and randomisation will be implemented based on a sequestered fixed randomisation schedule. Study centre personnel will call the IVRS once a subject has met all prerequisites for randomization; the IVRS will assign treatment.

Blinded study centre personnel will receive a randomisation notification indicating only the unique subject identifier and the date and time of randomisation. Each subject number will be a unique identifier. Once a subject number has been assigned, the number will not be reused even if the subject withdraws before receiving any investigational product. Details of the treatment assignment process are contained in the SRM.

### 5.3. Blinding

This is a double-blind study, neither the subject nor the study physician will know which of the two treatments (albiglutide or placebo) the subject is receiving.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency or in the event of a serious medical condition, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator**. Investigators have direct access to the subject's individual study treatment. It is preferred (but not mandatory) that the investigator first contacts the GSK Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment. If GSK study personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be fully documented in the appropriate data collection tool.

If a subject is unblinded by the investigator or treating physician then discontinuation of investigational product treatment for that subject will be at the discretion of the investigator. However, the subject should continue to be followed in the study (see Section 4.5).

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

### 5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned unused by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

### 5.5. Treatment Compliance

Subjects will be instructed to return all unused and used injector pens at the visits specified in the Time and Events Table (Table 1) in order to perform drug accountability and determine compliance. Subjects will be provided with a sharps container for the

disposal of used pens. To comply with health and safety considerations there will be no count made of used pens; only returned unused pens will be counted. In addition, subjects will be provided with a pre-printed card at each dispensing visit to record the date of each dose. The card is to be returned at the next dispensing visit with the unused pens.

## **5.6. Concomitant Medications and Non-Drug Therapies**

### **5.6.1. Permitted Medications and Non-Drug Therapies**

The usual care provider will manage the subjects according to standard of care, following local prescribing information. Close adherence to professional society guidelines for standard of care therapies in type 2 diabetes and cardiovascular disease will be emphasized during study conduct. Standard of care is described in greater detail in Section 3.2.

Unless specified as a prohibited medication in Section 5.6.2, all concomitant medications should be considered permitted provided they are not contraindicated for the individual subject concerned.

Like other members of the class, albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. This should be taken into account by investigators when prescribing concomitant medication.

It may be necessary to reduce the dose of concomitantly administered insulin secretagogues (such as SUs) or insulin to reduce the risk of hypoglycaemia when starting albiglutide.

All concomitant anti-hyperglycaemic medications (name of agent, total daily dose, start and stop dates) will be recorded in the eCRF at each visit. Concomitant cardiovascular medications taken during the study will also be recorded at each visit by class of agent. Additionally, all medications used within the 30 days prior to the onset and throughout the duration of an SAE, AE of special interest (Section 6.2.3), or an AE leading to discontinuation of investigational product will be recorded as individual agents, reason for use, together with start dates (and stop dates if applicable) and any changes since any previous AE.

### **5.6.2. Prohibited Medications and Non-Drug Therapies**

Subjects may not take a GLP-1 receptor agonist (other than blinded investigational product), nor any investigational drug, during the study (and any follow-up period after discontinuing investigational product).

If a subject receives a prohibited medication, a protocol deviation will be recorded.

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

Following the final study visit subjects will be contacted by telephone  $5 \pm 1$  weeks after last dose of study medication to assess any AEs ongoing since the last visit or newly emergent.

Subjects will be treated as deemed appropriate by the investigator following the end of the study. Investigational product will not be provided to subjects by GSK after the end of the study.

The half-life of albiglutide is approximately 5 days, and significant therapeutic concentrations can persist for 3 to 4 weeks after discontinuation. The choice of other medicinal products and dose selection should be considered accordingly, as adverse reactions may continue and efficacy may, at least partly, persist until albiglutide levels decline.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition whether or not GSK is providing specific post study treatment.

## **5.8. Treatment of Study Treatment Overdose**

No data are available with regard to albiglutide overdose in humans. The highest recommended dose of albiglutide is 50 mg once weekly.

During clinical studies of subjects with type 2 diabetes, the highest dose of albiglutide administered was 100 mg subcutaneously every four weeks for 12 weeks. This dose was associated with an increased frequency of nausea, vomiting, and headache.

There is no specific antidote for overdose with albiglutide. In the event of a suspected overdose, the appropriate supportive clinical care should be instituted, as dictated by the subject's clinical status. Anticipated symptoms of an overdose may be severe nausea, vomiting or headache. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the half-life of albiglutide (5 days).

## **6. STUDY ASSESSMENTS AND PROCEDURES**

The schedule of study assessments is shown in [Table 1](#). Detailed procedures for each assessment are provided in the SRM.

**Table 1 Time and Events Table**

Procedures <sup>1,2</sup>	Screening <sup>2</sup>	Randomization <sup>3</sup> /Baseline (can be same day as Screening Visit)	Study Drug Check Phone Call (4-6 wks post and.)	Clinic Visit Month 4 ± 18 days then every 8 months ± 18 days throughout the study	Unscheduled dose adjustment visit (if warranted)	Clinic Visit Month 8 ± 18 days then every 8 months ± 18 days throughout the study	Final study clinic visit <sup>4</sup> (or early withdrawal)	Post-Study Follow up Phone Call 5 ± 1 weeks after last IP dose
Written informed consent	X							
Review of Inc/excl criteria	X	X						
Demography & directed medical history	X							
Assessment of MACE and micro-vascular events				X		X	X	
HbA1c	X <sup>5</sup>			X		X	X	
Serum creatinine (eGFR)	X <sup>5</sup>					X	X	
Liver Function Tests <sup>6</sup>		X				X	X	
Genetic sampling <sup>7</sup>		X						
Patient reported outcomes questionnaires <sup>8</sup>		X				X	X	
Key concomitant non-diabetes medication		X		X		X	X	X
Diabetes medication		X		X		X	X	X
Study drug reminder			X	X	X	X		
Physical examination <sup>9</sup>		X				X	X	
SAEs, AEs of special interest, AEs leading to IP discontinuation		X	X	X		X	X	X
Pregnancy test <sup>10</sup>	X	X						
Study drug dispense/compliance <sup>11</sup>		X		X	X	X	X	

- Subjects who discontinue investigational product should be handled as described in Section 4.4.
- Assessments per the Month 4 visit will alternate with those per the Month 8 visit throughout the study i.e., assessments at months 4, 12, 20 etc will be per Month 4; those at month 8, 16, 24 etc..will be per Month 8.
- Screening and Randomisation can occur at the same visit if all eligibility information is available. If Screening and Randomisation occur at the same visit assessments should not be duplicated.
- Once it is projected that the target number of MACE events will have been collected, a 3 month window will be defined for conducting the final, face to face visit.
- HbA1c and creatinine assessed using local laboratories at Screening visit and measured no more than 6 months prior to randomisation. If HbA1c or creatinine have not been assessed in the previous 6 months assessments to be performed via a central laboratory and results available prior to randomization. The investigator has the discretion to repeat screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.
- Liver function tests: ALT, AST, alkaline phosphatase, bilirubin, GGT. Blood samples for LFTs at randomization must be collected prior to the first dose of investigational product.
- Informed consent for genetic research must be obtained before collecting a sample. Genetics sample can be collected at any time after genetic consent has been obtained and the subject has been randomised.
- TRIM-D, EQ-5D and study specific questionnaire (details in Section 6.3).
- See Section 6.2.7.
- Only applies to women of child bearing potential. At screening perform urine pregnancy test. If positive, send serum sample to the central laboratory for confirmation. At Randomisation perform a urine pregnancy test. If result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised. If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. See Section 6.2.6.
- Study drug dispensing not performed at final visit, compliance check not performed at Screening.

## 6.1. Critical Baseline Assessments

Disease, and therapy history, including cardiovascular medical history/risk factors will be assessed at Baseline. Investigators are encouraged to implement lifestyle modifications and adjust or initiate the appropriate pharmacotherapy throughout the study as recommended by current locally followed therapeutic cardiovascular and diabetes guidelines for participants in the study. Screening and randomisation can occur at the same visit depending on availability of information to determine eligibility of the subject to enter the study.

## 6.2. Safety

The following sections provide further detail on the safety assessments. Planned time points for all safety assessments are listed in the Time and Events Table ([Table 1](#)). Unscheduled visits will occur as medically necessary. Detailed procedures for obtaining each assessment are provided in the SRM.

Safety endpoints are described in [Section 2](#) and will include monitoring of cardiovascular events ([Section 6.2.1](#)), deaths, AEs of special interest ([Section 6.2.3](#)), clinically significant microvascular events ([Section 6.2.4](#)), SAEs and AEs leading to discontinuation of investigational product.

Liver chemistry stopping and follow-up criteria and AEs are described in [Section 4.4.3](#) and [Appendix 3](#).

### 6.2.1. Cardiovascular Events

Events referred to the CEC by the investigator as potential endpoints or transient ischemic attacks (TIAs) will not be collected or reported as SAEs, regardless of the adjudication outcome ([Section 6.2.2](#)). These events will be reviewed by an Independent Data Monitoring Committee ([Section 9.8](#)).

The CEC will review and adjudicate the following clinical events:

- Myocardial infarction
- Stroke
- Unstable angina requiring revascularization
- Hospitalization for heart failure
- Sudden cardiac death
- TIA
- In addition, all clinical events submitted for adjudication and all other SAEs with a fatal outcome will be reviewed and adjudicated to classify the cause of death as cardiovascular or non-cardiovascular.

When the local investigator reported event and the CEC decision on the nature of the event differ, the CEC's decision will be considered final. The detailed descriptions of the



endpoint (and TIA) definitions necessary for adjudication are contained within the CEC Charter (available on request). The guiding principle will be the “2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular and Stroke End Point Events for Clinical Trials” [ACC/AHA, 2014] and the “Third Universal Definition of Myocardial Infarction” endorsed by the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation (WHF) [Thygesen, 2012].

Source documentation required to support the adjudication of the events is described in the SRM. Recording of potential endpoint and TIA events in the eCRF and submission of source documentation will be required for clinical events meeting reporting criteria whether or not an endpoint event is suspected by the investigator.

#### **6.2.1.1. Other CV Events**

GSK has identified other CV events of special interest for all clinical studies. Investigators will be required to fill out event specific data collection tools for the following cardiovascular events which meet SAEs criteria or are non-serious events that result in discontinuation of investigational product:

- Arrhythmias (other than atrial fibrillation/flutter, see Section 6.2.3)
- Valvulopathy
- Pulmonary hypertension
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation (other than urgent revascularisation for unstable angina, a component of a secondary endpoint)

This information should be recorded in the specific cardiovascular eCRF within one week.

#### **6.2.2. Adverse Events (AE) and Serious Adverse Events (SAEs)**

The definitions of an AE or SAE can be found in [Appendix 5](#).

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

For this study events of myocardial infarction, stroke, unstable angina requiring urgent revascularization, hospitalization for heart failure, TIA and sudden cardiac death will not be collected or reported as AEs or SAEs. These events will be collected separately, subjected to blinded adjudication by an independent CEC using prespecified diagnostic criteria, and reported separately (Section 6.2.1.1). All other events that meet serious criteria as defined in [Appendix 5](#) should be reported as SAEs.

All events with an outcome of death will be adjudicated to classify the cause of death as specifically cardiovascular or non-cardiovascular. Any event resulting in death should be

reported as a SAE unless the event is myocardial infarction, stroke, unstable angina w/ urgent revascularization, Heart failure, TIA or sudden cardiac death which the protocol specifies are not to be collected as adverse events.

The study will not collect all non-serious AEs. Non-serious AEs leading to discontinuation of investigational product and non-serious AEs of special interest (see Section 6.2.3) will be collected.

Any events not specifically addressed above should be reported as an AE or SAE according to the definitions in [Appendix 5](#).

#### **6.2.2.1. Time period and Frequency for collecting AE and SAE information**

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 6.2.2.3), at the timepoints specified in the Time and Events Table ([Table 1](#)).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in [Appendix 5](#).
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in [Appendix 5](#).

#### **6.2.2.2. Method of Detecting AEs and SAEs**

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

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

Additionally subjects will be asked specific questions about the occurrence of AEs of special interest (Section 6.2.3).

#### **6.2.2.3. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 6.2.3) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 4.5). Further information on follow-up procedures is given in [Appendix 5](#).

#### **6.2.2.4. Sentinel Events**

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/severe neutropenia
- Anaphylaxis and anaphylactoid reactions (see also Section 6.2.3)
- Hepatotoxicity (see also Section 6.2.3)
- Acute renal failure
- Seizure
- Stevens Johnson syndrome/toxic epidermal necrosis

#### **6.2.2.5. Regulatory Reporting Requirements for SAEs**

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

### **6.2.3. Adverse Events of Special Interest**

The investigator or site staff will be responsible for detecting, documenting and reporting events the following AEs of special interest:

- Development of thyroid cancer
- Haematologic malignancy
- Pancreatic cancer
- Pancreatitis
- Injection site reactions
- Immunological reactions (e.g., drug hypersensitivity reactions involving anaphylaxis/anaphylactoid reactions, acute bronchoconstriction, angioedema, and/or acute urticaria)
- Severe hypoglycaemia events (which includes all events meeting the definition of SAEs [Appendix 5](#))
- Hepatic events
- Hepatic enzyme elevations (including GGT)
- Serious GI events
- Appendicitis
- Atrial fibrillation/flutter
- Pneumonia
- Worsening renal function
- Diabetic retinopathy

The results of any investigation should be recorded in the relevant sections of the subjects' eCRFs. In addition, for thyroid, pancreas or haematological malignancies a copy of the histopathology report and a discharge summary if the subject was admitted, or any available case summary (e.g. clinic letter), is to be provided to the Sponsor, if available.

Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. In subjects where a treatment emergent thyroid nodule is identified, if serum calcitonin is measured at the discretion of the Investigator (e.g., per local guidelines) and found to be >100 ng/L this should prompt further investigation for MTC and potential interruption or discontinuation of investigational product until diagnosis has been resolved. If MTC or other thyroid C-cell neoplasia is diagnosed, albiglutide will be discontinued.

A Pancreatitis Adjudication Committee composed of independent specialists in gastroenterology will review all cases of possible pancreatitis.

Subjects should also be closely monitored for signs of potential allergic or drug hypersensitivity reactions including anaphylaxis, angioedema, generalized urticaria, and other potential manifestations of systemic allergic or drug hypersensitivity reactions. A serum sample should be taken as soon as possible after any such event in order to measure antibody to the drug. Instructions for sample processing are in the SRM. These events should be reported as AEs or SAEs based on the clinical evaluation of the subject. The reactions should be followed to completion as typical for any AE or SAE. Subjects with allergic or drug hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology should have investigational product withdrawn and not re-introduced.

Episodes of severe hypoglycaemia will be recorded according to subject report. Severe hypoglycaemic incidents will be defined as those episodes of hypoglycaemic symptoms for which the subject required assistance from another person and from which the subject recovered promptly after oral carbohydrate, intravenous glucose, glucagon administration or other resuscitative actions (definition per ADA Workgroup on Hypoglycaemia [Sequist, 2013]). Additionally, all episodes of hypoglycaemic symptoms which in the investigator's opinion meet the definition of a SAE (defined in [Appendix 5](#)) will be included as severe hypoglycaemic episodes. During this study, if a subject's eGFR approaches 30mL/min/1.73m<sup>2</sup> closer monitoring of renal function is considered prudent, according to standard clinical practice. If eGRF is <15mL/min/1.73m<sup>2</sup> follow the procedure set out in Section [4.4.4](#).

#### **6.2.4. Clinically Important Microvascular Events**

Clinically important microvascular events are defined as the following: need for renal transplant or dialysis, new diabetes-related blindness, and procedures (laser photocoagulation or anti-vascular endothelial growth factor treatment or vitrectomy for diabetic retinopathy/eye disease). Clinically important microvascular events will be reported as recorded in the eCRF by the investigator without adjudication.

The AEs associated with the above outcomes or treatments should be reported separately as an AE or SAE according to the definitions in [Appendix 5](#).

#### **6.2.5. Pregnancy**

- If a subject becomes pregnant during the study they should discontinue Investigational Product.
- Details of all pregnancies in female subjects will be collected after the start of dosing and until the end of the Post-treatment Follow-up Period.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in [Appendix 6](#).

### **6.2.6. Clinical Laboratory Assessments**

All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Table 1). Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all central laboratory safety parameters will be provided to the site.

If additional non-protocol specified laboratory assessments result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE of special interest or dose modification) the results must be recorded in the CRF.

Refer to the SRM/laboratory manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

The following laboratory assessments will be performed: serum creatinine, HbA1c, liver function tests [AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin, GGT], and urine and serum  $\beta$ hCG pregnancy test (for women of child bearing potential). All study-required laboratory assessments will be performed by a central laboratory, with the exception of HbA1c and creatinine at Screening and urine pregnancy test at Screening/Randomization.

#### **Screening HbA1c and serum creatinine**

Screening HbA1c and serum creatinine values should be based on the most recent local laboratory values taken as part of usual care within the previous 6 months and the values entered into the eCRF. These assessments must have been performed at an accredited laboratory. HbA1c screening results must be either Diabetes Control and Complications Trial (DCCT) aligned or International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardized. HbA1c screening results from point of care equipment are acceptable provided that the equipment is maintained by an accredited laboratory. If HbA1c or creatinine have not been assessed in the previous 6 months, laboratory assessments will be performed via the central laboratory to determine eligibility (if a local laboratory is used in error the results are acceptable for determining eligibility). The investigator has the discretion to repeat screening HbA1c, and/or creatinine, based on clinical rationale even if previously available local results meet the eligibility criteria to allow the investigator to accommodate the possibility of change between screening and randomisation.

Re-screening of subjects who did not meet the eligibility criteria for HbA1c or creatinine based on local laboratory values taken as part of usual care is permitted. If values were based on laboratory results as part of usual care then one re-test is permitted within the protocol at Screening. Any future re-screening will be based on laboratory results obtained as part of usual care.

**Pregnancy testing (for women of childbearing potential)**

At the screening visit perform a urine pregnancy test. If the urine pregnancy test is positive, send a serum blood sample to the central laboratory for confirmation of pregnancy.

At the Randomisation visit perform a urine pregnancy test. If the result is positive do not randomize the subject. If the urine pregnancy test is negative then the subject can be randomised (provided all other eligibility criteria have been met).

If Screening and Randomisation are to take place at the same visit then follow the instructions for Screening. Do not randomise if the urine pregnancy test is positive; send a serum blood sample to the central laboratory for confirmation of pregnancy. If the urine pregnancy test is negative then the subject can be randomised at the same visit (provided all other eligibility criteria have been met).

**6.2.6.1. Estimated Glomerular Filtration Rate (eGFR)**

Serum creatinine will be measured every 8 months by a central laboratory. It will be used to calculate eGFR using the MDRD formula [Levey, 2009], namely:

$$\text{eGFR (ml/min/1.73m}^2\text{)} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}).$$

**6.2.7. Physical examination**

A general physical examination, including height and neck (thyroid), will be performed at randomization. A targeted physical examination will be performed at all other time points as specified in the Time and Events Table (Table 1). The targeted physical examination will evaluate the cardiovascular system and injection sites and will include measurement of blood pressure and heart rate taken with the subject either in a semi-recumbent or seated position after at least a 5-minute rest period.

**6.3. Value Evidence and Outcomes****6.3.1. Value Evidence and Outcomes Assessments****6.3.1.1. Treatment Related Impact Measure – Diabetes (TRIM-D)**

In order to evaluate satisfaction with treatment and to compare satisfaction across treatment groups, the TRIM-D questionnaire will be self administered by all subjects at baseline and at each 8 month visit (and, to the extent possible, at the time of study completion or withdrawal from the study).

The TRIM-D, developed in 2009, is a 28-item treatment satisfaction measure scored to produce 5 sub-scale scores (Treatment Burden, Daily Life, Diabetes Management, Psychological Health, and Compliance) as well as a total score. It is available in a wide range of translations.



The TRIM-D development, in accordance with the principles of the Food and Drug Administration Patient Reported Outcome Guidance document, was based on findings from the published literature including content from already-existing treatment satisfaction measures as well as significant input from subjects with type 1 and with type 2 diabetes and from expert diabetes clinicians. The TRIM-D has been evaluated in a sample of 507 subjects (74% with type 2 diabetes) and has been shown to have acceptable reliability and validity [Brod, 2009a]. Its responsiveness was also evaluated in a sample of 242 subjects (71% with type 2 diabetes) and found to be acceptable [Brod, 2009b]. Some preliminary work has been done on estimating its minimal important difference but this needs further exploration [Brod, 2009b].

#### **6.3.1.2. EQ-5D**

The EQ-5D will be self-administered by subjects in order to measure generic health status. Combining the EQ-5D with the disease-specific TRIM-D, which is designed to have maximum sensitivity to relevant aspects of disease related treatment, will provide a more robust evaluation of the impact of treatments for type 2 diabetes and allow for clearer interpretation of study results. TRIM-D results, if consistent with the general trends seen in the EQ-5D, will have enhanced credibility.

The EQ-5D is a standardized instrument used to evaluate generic health-related quality of life. It is applicable to a wide range of health conditions and treatments, and it provides a simple descriptive profile and a single index value for health status. It is also used to provide utilities, or preference weights, for use in economic (cost effectiveness) evaluations. It is available in 141 self complete official language versions.

The EQ-5D has been used extensively in studies to measure the impact of type 2 diabetes and treatments for the disease. A systematic review identified 54 publications reporting EQ-5D responses and 39 papers presenting evidence on the measurement properties of the EQ-5D in this population [Janssen, 2011]. This evidence supported the validity, reliability, and responsiveness of the EQ-5D for evaluating health-related quality of life in subjects with type 2 diabetes. Other studies reported that index scores from the EQ-5D have been shown to be an independent predictor of the risk of mortality, future vascular events, and other complications in people with type 2 diabetes [Clarke, 2009]. In addition, the SHIELD longitudinal study (1,741 respondents with type 2 diabetes and 4,543 without diabetes) used the EQ-5D to assess the 5-year changes in health-related quality of life in type 2 diabetes [Grandy, 2012].

#### **6.3.1.3. Exploratory Diabetes Management Questions**

In addition to the standardised instruments described above, patient experience in relation to the management of their diabetes will be evaluated in a subset of sites using a small number of self-administered diabetes management questions. These types of customized questions have been used successfully in asthma and in diabetes when patients are involved with goal-setting [Juniper, 1992; Anderson, 2010]. This tailored approach is an opportunity to capture data in the study that are not otherwise available from standard PRO measures such as the TRIM-D and the EQ-5D. As an exploratory endpoint, this set of questions (3 items at baseline, and at each 8 month follow-up visit) imposes very little patient or site burden, but can offer critical insight into the one area of the patient's



choosing that s/he finds most difficult to manage. In addition, this patient-centred endpoint has the potential to be sensitive to changes over time.

These questions have been developed by GSK based on factors identified as important to subjects in the development of published, validated and reliable subject reported outcomes instruments in type 2 diabetes.

#### **6.3.1.4. Healthcare Resource Utilisation**

Data will be collected on the following healthcare resource use:

- All cause hospitalisations and related healthcare resource use.

Healthcare resource use data will be collected in order to facilitate subsequent health-economic analyses comparing costs between albiglutide added to standard of care and placebo added to standard of care (cost is not an end point in the study).

Data on all-cause hospitalizations and related inpatient healthcare resource use will be collected. This will include:

- All-Cause hospitalisation including: Admission and discharge diagnoses (primary and secondary), length of stay, level/type of ward, and time spent in Intensive Therapy Unit (or equivalent).

#### **6.4. Genetic Research**

Information regarding genetic research is included in [Appendix 1](#).

### **7. DATA MANAGEMENT**

- For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

## **8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS**

### **8.1. Hypotheses**

This trial will examine the following primary question:

- Whether albiglutide is non inferior by a margin of 1.3 with respect to its effect on adjudicated MACE, when added to glycaemic standard of care, versus standard of care alone. Letting  $\lambda_1$  = hazard ratio for time to first MACE for albiglutide vs placebo, then:

Null hypothesis:  $\log \lambda_1 \geq \log(1.3)$

Alternative hypothesis:  $\log \lambda_1 < \log(1.3)$

### **8.2. Study Design Considerations**

#### **8.2.1. Sample Size Assumptions**

The primary outcome will be analyzed such that the overall Type 1 error is no greater than 5% (two-sided). Specifically, the non-inferiority assessment of albiglutide compared to placebo will be conducted at 0.05 level, requiring one-sided significance at 0.025.

The power for MACE non-inferiority is calculated via the asymptotic variance and normality of the maximum likelihood estimator for the log-hazard ratio. Assuming a true hazard ratio of 1.0, 611 events will be needed to have 90% power to rule out non-inferiority margin of 1.3 for the hazard ratio with type I error of 0.05. The study duration will be event-driven. A total of 9400 subjects will be enrolled and followed until it is projected that approximately 611 adjudicated MACE events will have occurred. If the observed rate for MACE is 2.0% or 3.0%, the mean follow-up will be 3.2 or 2.2 years respectively, assuming that the number of subjects lost to follow-up accounts for 1% or less.

#### **8.2.2. Sample Size Sensitivity for MACE non-inferiority**

9400 subjects will be enrolled to cumulate the first MACE events experienced by 611 unique subjects. The study duration may vary depending on actual MACE event rate and duration of enrolment period.

**Table 2 Total Study Duration Sensitivity for Varying MACE Event Rate and Duration of Recruitment**

MACE rate (% pa)	Duration of recruitment			
	1.5 yrs	2.0 yrs	2.5 yrs	3.0 yrs
2.0	4.1yrs	4.4yrs	4.6yrs	4.9yrs
2.5	3.4 yrs	3.7yrs	3.9yrs	4.2yrs
3.0	3.0yrs	3.2yrs	3.5yrs	3.8yrs
3.5	2.7yrs	2.9yrs	3.2yrs	3.4yrs

### 8.2.3. Sample Size Re-estimation

The aggregate blinded event-rate data will be periodically reviewed by the Executive Committee and the sponsor. The study has an event-driven design. Should emerging data diverge significantly from protocol assumptions, the total sample size and/or follow up time may be adjusted, within the bounds of feasibility, to achieve the event target.

## 8.3. Data Analysis Considerations

### 8.3.1. Analysis Populations

The intent-to-treat (ITT) population will include all randomly assigned subjects. The ITT subjects will be analyzed according to randomised treatment. The inference for primary objectives in the study will be made from ITT population.

Per-protocol Population (PP) will exclude the subjects who have major protocol violations. Per-protocol analysis will include Per-protocol population only and their data upon to the time of discontinuation of investigational product plus 56 days.

The non-insulin population (NI) will include all subjects in the ITT population who are not on insulin at baseline. Inference for the time to insulin endpoint will be made from the NI population.

The baseline basal insulin user population (BI) will include all subjects in the ITT population who are on basal insulin, but not on other insulin at baseline. Inference for the time to prandial insulin endpoint will be made on BI population.

The safety population will include all enrolled subjects who receive at least 1 dose of study treatment. The safety population subjects will be analyzed according to the treatment received. The safety population will be used for analyses of safety objectives.

Other analysis populations will be defined in the RAP.

### **8.3.2. Analysis Data Set**

For time to event data, censoring time for subjects who lost to follow-up is defined as following:

- For primary analysis, subjects who are lost to follow-up will be censored at the date of last evidence of confirmatory status for MACE events.
- For on-treatment analysis, censoring date will be the last dose date.
- For on-therapy analysis (on-treatment+56 days), censoring date will be the last dose date+56 days.
- For analysis of all cause of mortality, censoring date will be the latest date known alive.

### **8.3.3. Treatment Comparisons**

Demographic and baseline characteristics (e.g., gender, age, racial or ethnic origin, height and weight, body mass index (BMI), blood pressure and other characteristics) will be summarized for each treatment group. In addition, smoking and alcohol habits, diabetic and cardiovascular medical history, baseline laboratory results, and prior medications will be summarized by treatment group. Binary and ordinal characteristics will be summarized by counts and percentages, while continuous variables will be represented by mean and standard deviations or medians and percentiles, as appropriate. Any variables with treatment imbalances may be considered as covariates for further analysis of an exploratory nature. Such covariates will be identified on the basis of the clinical relevance of the observed treatment difference.

#### **8.3.3.1. Primary Comparisons of Interest**

The primary endpoint will be the time to the first occurrence of MACE over the full duration of the study. A p-value for the primary endpoint will be calculated from a Cox regression model with treatment group as the only covariate for the hypotheses described in Section 8.1.

#### **8.3.3.2. Other Comparisons of Interest**

For other analyses incidence rates will be presented for binary data and summary statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous data. Furthermore, summary statistics of change from baseline for HbA1c will be presented along with percent of subjects within ranges of clinical interest (e.g., HbA1c < 7.0%).

### **8.3.4. Interim Analysis**

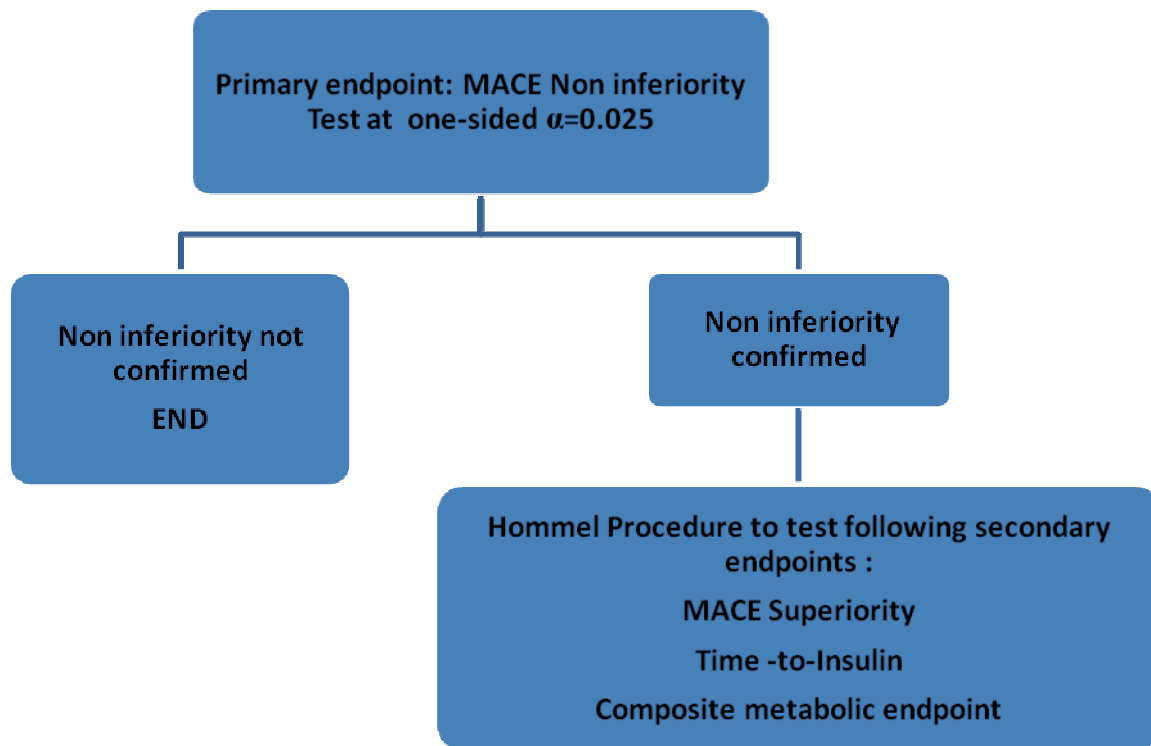
An IDMC will monitor progress of the study and ensure that it meets the highest standards of ethics and subject safety. All cardiovascular event data, together with other safety data, will be sent to the IDMC for review at approximately every 6 months after the first subject has been randomised to receive treatment. This frequency may be

adjusted, if deemed necessary by the IDMC, depending on the enrolment rates and the rate of safety events. There are no plans to stop the study early for a non-inferiority or benefit claim, however should the IDMC identify in the course of its scheduled reviews overwhelming evidence of MACE benefit (e.g.,  $p < 0.001$ ), with directionally consistent findings on all-cause mortality, the IDMC might consider recommending early stopping. This approach essentially preserves the final alpha for the end-of-study analysis at 5% and hence there are no plans to adjust the final alpha on account on safety reviews conducted by the IDMC. The IDMC charter, reporting and procedures are outlined in separate documents.

### **8.3.5. Multiplicity Controls**

A multiple comparisons adjustment strategy will be implemented for the multiple inferential tests among the primary endpoint and secondary endpoints of MACE superiority, time to insulin and composite metabolic endpoint.

The strategy will use a combination of gatekeeper and Hommel procedure. The first step is to evaluate the MACE non-inferiority of the albiglutide group vs the placebo group at a one-sided  $\alpha=0.025$  level. If the result of non-inferiority is significant, MACE superiority, time-to-insulin and composite metabolic endpoint will be tested simultaneously using the Hommel procedure with  $\alpha=0.05$ . The above multiplicity control approach will preserve the study's nominal significance level of 0.05. The test order is illustrated in the diagram below.



Hommel Procedure for secondary endpoints is described below:

Three hypothesis tests for MACE superiority, time-to-insulin, and composite metabolic endpoint are subject to be adjusted by the Hommel procedure. Let  $P(1)$ ,  $P(2)$  and  $P(3)$  represent the ordered p-values that  $P(3) > P(2) > P(1)$  and  $H(1)$ ,  $H(2)$  and  $H(3)$  are corresponding hypotheses.

If  $P(3) < 0.05$ , reject  $H(3)$ ,  $H(2)$ ,  $H(1)$ . End of test.

If  $P(3) \geq 0.05$  and  $P(2) < 0.05/2$ , accept  $H(3)$ , reject  $H(2)$ ,  $H(1)$ . End of test.

If  $P(3) \geq 0.05$  and  $P(2) \geq 0.05/2$  and  $P(1) < 0.05/3$ , accept  $H(3)$ ,  $H(2)$ , reject  $H(1)$ . End of test.

If  $P(3) \geq 0.05$ ,  $P(1) \geq 0.05/3$  and  $0.05/2 \leq P(2) < 0.05 \cdot 2/3$ , accept  $H(3)$ ,  $H(2)$ , reject  $H(1)$ . End of test.

If  $P(3) \geq 0.05$ ,  $P(2) \geq 0.05 \cdot 2/3$  and  $P(1) \geq 0.05/3$ , accept  $H(3)$ ,  $H(2)$  and  $H(1)$ .

*Other Secondary Endpoints and Subgroup Analysis*

The following secondary endpoints will provide supportive evidence for cardiovascular safety and will not use any multiplicity adjustment procedure.

- Components of primary endpoint (MACE = cardiovascular death, MI, stroke)
- MACE + urgent revascularisation for unstable angina
- Cardiovascular death or hospitalisation for heart failure

Other secondary endpoints which do not qualify for formal statistical hypothesis testing will be analyzed and have results presented with confidence interval and nominal p-values:

- Mean HbA1c at scheduled visits and change from baseline
- Mean body weight at scheduled visits and change from baseline
- Mean eGFR at scheduled visits and change from baseline
- Time to initiation of prandial insulin
- Composite microvascular endpoint

To examine the degree of consistency of the overall treatment effect in terms of important prognostic factors, subgroup analyses of the primary outcomes will be performed based on subject demographics and baseline characteristics. These exploratory subgroup analyses will not be adjusted for multiple comparisons and will be interpreted descriptively.

**8.3.6. Key Elements of Analysis Plan**

Any deviations from the original analysis planned in the protocol agreed upon prior to finalization of the RAP, will be described in that document. Any additional changes to the planned analysis in the RAP will be described in the final clinical study report.

**8.3.6.1. Primary Analysis**

The primary analysis is an ITT analysis of the time to the first occurrence of MACE over the full duration of the study. Time to event analyses will be performed using Cox's Proportional Hazard regression with SAS PHREG with treatment group as the only covariate. Data for subjects without a primary event will be censored.

Treatment differences will be estimated via the hazard ratio and its 95% confidence interval (CI).

The hypothesis of non-inferiority of albiglutide relative to placebo group with hazard ratio less than 1.3 with respect to cardiovascular risk will be tested at the end of the study when ~611 first MACE events are cumulated.

The strength of evidence for non-inferiority will be determined by testing the hypothesis that the observed hazard ratio is significantly different from the null margin of 1.3 (one-sided  $p < 0.025$  for such a test being equivalent to the upper 95% confidence limit after multiplicity adjustment for the hazard ratio being less than 1.3). The absolute risk difference per 100 PY and superiority p-value for albiglutide vs. placebo will also be presented.

The product-limit estimates of the probabilities (and their standard errors) of first MACE over time will be computed and displayed as Kaplan-Meier (KM) survival curves for albiglutide and placebo groups. The KM curves will also be presented corresponding to the above comparisons.

The total number of all MACE or any of its components will be analyzed by Poisson regression model. The incidence rate per 100 person-years, relative risk and their 95% CI will be presented. Number of subjects who experienced at least one event, 2 or 3 or more MACE or its components will also be summarized by treatment group.

As sensitivity analyses, the analyses described above will be repeated using events occur while on-treatment and events occur during the period of on-treatment plus 56 days post last dose.

#### **8.3.6.2. Secondary Endpoint Analysis**

Endpoints that supplement the primary objective by further characterization of the effects of albiglutide on cardiovascular outcomes endpoints:

- MACE superiority will be evaluated using the same Cox regression model as the primary analysis of MACE non-inferiority.
- Supportive endpoints including the time to first occurrence of adjudicated MACE or urgent revascularisation for unstable angina, time to first occurrence of individual components of MACE, time to first occurrence of cardiovascular death or hospitalisation for heart failure will be analyzed using a proportional Cox regression model similarly as the primary endpoint.

Endpoints that evaluate the effects of albiglutide on metabolic management of type 2 diabetes:

- Among the subjects who are not on insulin at baseline (NI population), time to insulin will be analyzed using a proportional Cox regression model similar to the primary MACE analysis. The product-limit estimates of the probabilities (and their standard errors) of adding insulin over time will be computed and displayed as Kaplan-Meier (KM) survival curves for albiglutide and placebo treatment groups. The KM curves will also be presented corresponding to the above comparisons.
- Composite of the proportion of those achieving good control ( $HbA1c \leq 7.0\%$ ) AND no severe hypoglycaemic incidents AND weight gain  $<5\%$  at the end of the study would be evaluated utilize nonparametric, covariance-adjusted, extended Mantel-Haenszel tests. Additional analysis will be provided for scheduled visits. Nominal p-values and 95% CIs will be presented for these visits. Time to introduction of



prandial insulin in those on basal insulin  $\pm$  orals anti-hyperglycemic drugs at baseline will be analyzed using PH model / log-rank test and KM method similar to the primary endpoint.

- Composite of microvascular events will be analyzed using a proportional Cox regression model / log-rank test and KM method similar to the primary endpoint.
- HbA1c, body weight and eGFR will be analyzed using a repeated mixed effect model. The least square means, 95% CIs and nominal p-values will be presented.
- Additional analysis will be performed to assess the incidence rate of recurrent severe hypoglycaemic events between treatment groups during the course of the study. A repeated Poisson regression model including treatment and visit as factors will be used to test treatment difference with offset for person years. An unstructured working correlation matrix will be used in the iterative estimation process. The model-adjusted least square incidence rate for each treatment as well as the treatment difference of the incidence rate will be reported. Events of severe hypoglycaemia will also be summarized descriptively by treatment group. Additional summary by baseline HbA1c, renal status and age subgroup will also be provided.

Further analysis details will be provided in the RAP.

#### **8.3.6.3. Subgroup Analysis**

Separate subgroup analyses of the primary outcomes will be performed based on subject demographics and baseline characteristics. Subgroups may include sex, age group, BMI, whether subjects have history of a previous cardiovascular event, and baseline HbA1C, background of anti-hyperglycaemia treatment etc. The detail of subgroups will be pre-specified in the RAP. Consistency of treatment effects will be assessed using Cox regression, along with the 95% confidence intervals for the relative risk or hazard ratios for each subgroup a nominal alpha level for interaction of 0.10 will be used. The effect of treatment interaction with subgroups will also be explored; however as the number of these subgroup variables may be large, the probability of observing at least one statistically significant result may be high. Thus these additional analyses will be considered exploratory regardless of the p-value associated with any interaction.

Further details will be provided in the RAP.

#### **8.3.6.4. Other Safety Analyses**

Subject demographics, medical history, prior and concomitant medications, vital sign measurements, laboratory values, physical examination assessments, will be summarized by treatment group using descriptive statistics.

For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages.

For SAEs, AEs leading to withdrawal and AEs of special interest occurring after discontinuation of investigational product, the number and percentage of subjects, total number of events, incidence density and event rate will be presented by treatment group and overall at the SOC, High Level Term and Preferred Term (PT) level. Relative Risk for each event and its 95% CI will also be presented. The time to first occurrence of the specific events and the time of the event with respect to the preceding dose of study medication will be summarized.

All cause mortality will be summarized by treatment group and analyzed using PH model similarly as the-primary endpoint.

All events sent to CEC (including TIAs) will be grouped by type based on the standard MedDRA queries that correspond to cardiovascular and cerebrovascular events. Adjudication results will be summarized by event type and treatment group. A by subject listing of these events will be generated. The listing will include seriousness, severity, whether event is a reason for early study drug discontinuation or study withdrawal, and adjudication results.

Pancreatitis events will be adjudicated by the independent Pancreatitis Adjudication Committee. The information for investigator reported pancreatitis events and its adjudication results will be provided.

Further analysis details will be provided in the RAP.

#### **8.3.6.5. Value Evidence and Outcomes Analyses**

TRIM-D total score and score for each domain will be summarized descriptively by treatment group and scheduled visit. Score changes from baseline will be compared between treatments for each visit by ANCOVA an model

For EQ-5D, subjects' responses at each visit for the 5 domains will be summarized categorically by treatment group, together with the summary of utility score at each visit and change from baseline by treatment group. Change from baseline will be compared between treatment groups for each visit by an ANCOVA model.

For study specific PRO questions, responses will be summarized descriptively by treatment group and scheduled visit.

Healthcare resource use will be summarized by treatment group and visit.

Further analysis details will be provided in the RAP.

## **9. STUDY CONDUCT CONSIDERATIONS**

### **9.1. Posting of Information on Publicly Available Clinical Trial Registers**

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

## **9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process**

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

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH E6 Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favourable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

Signed informed consent must be obtained for each subject prior to participation in the study

The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research. Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission. Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

## **9.3. Quality Control (Study Monitoring)**

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

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

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

#### **9.4. Quality Assurance**

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

#### **9.5. Study and Site Closure**

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

## **9.6. Records Retention**

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

## **9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication**

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

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

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.

### **9.8. Independent Data Monitoring Committee (IDMC)**

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter.

### **9.9. Pancreatitis Adjudication Committee**

Detailed information on suspected pancreatitis events will be collected on special pages of the eCRF. A Pancreatitis Adjudication Committee composed of independent specialists in gastroenterology will review cases of possible pancreatitis. Details of this committee and case adjudication are described in the committee's charter available on request.

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## 11. APPENDICES

### 11.1. Appendix 1: Genetic Research

#### Background

Genetics is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of genetic associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	<i>HLA-B*57:01</i> (Human Leukocyte Antigen B)	Carriage of the <i>HLA-B*57:01</i> variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective <i>HLA-B*57:01</i> screening and exclusion of <i>HLA-B*57:01</i> positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labelling in the United States and Europe now recommend (US) or require (EU) prospective <i>HLA-B*57:01</i> screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. <i>HLA-B*57:01</i> screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.

Drug	Disease	Gene Variant	Outcome
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	<i>HLA-B*15:02</i>	Independent studies indicated that patients of East Asian ancestry who carry <i>HLA-B*15:02</i> are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of <i>HLA-B*15:02</i> prior to initiating treatment with carbamazepine.
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	<i>UGT1A1*28</i>	Variations in the <i>UGT1A1</i> gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular <i>UGT1A1</i> gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the <i>UGT1A1*28</i> variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful genetic research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable genetic analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to albiglutide.

### Genetic Research Objectives

The objective of genetic research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to albiglutide. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with albiglutide, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Safety and/or tolerability
- Efficacy

### **Study Population**

Any subject who is enrolled in the clinical study, can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from genetic research.

Subject participation in the genetic research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

### **Study Assessments and Procedures**

Blood samples can be taken for deoxyribonucleic acid (DNA) extraction and used in genetic assessments.

If taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (~6ml) will be collected for the genetic research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomised and provided informed consent for genetic research, but may be taken at any time while the subject is participating in the clinical study.

- The genetic sample is labelled (or “coded”) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilise the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct genetic analysis may be identified after a study (or a set of studies) of albiglutide has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to albiglutide.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

## Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in genetic research with the genetic sample retained for analysis
- Withdraw from genetic research and destroy the genetic sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time when a subject wishes to withdraw from genetic research or have their sample destroyed whether during the study or during the retention period following close of the main study.

## Screen and Baseline Failures

If a blood sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

## Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to albiglutide. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and genetic research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data.

Results of genetic investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

### **Informed Consent**

Subjects who do not wish to participate in genetic research may still participate in the clinical study. Genetic informed consent must be obtained prior to any blood being taken for genetic research.

### **Provision of Study Results and Confidentiality of Subject's Genetic Data**

GSK may summarise the genetic research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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## 11.2. Appendix 2: GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

1. Contraceptive subdermal implant that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label.
2. Intrauterine device or intrauterine system that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Trussell, 2011]
3. Oral Contraceptive, either combined or progestogen alone [Trussell, 2011]
4. Injectable progestogen [Trussell, 2011]
5. Contraceptive vaginal ring [Trussell, 2011]
6. Percutaneous contraceptive patches [Trussell, 2011]
7. Male partner sterilization prior to the **female subject's entry** into the study, and this male is the sole partner for that subject. The information on the male sterility can come from interview with the subject on her male partner's medical history.
8. Male condom **combined with a female** diaphragm, with or without a vaginal spermicide (foam, gel, film, cream, or suppository). In the UK it is a country-specific requirement of the regulatory authority (Medicines and Healthcare Products Regulatory Agency) that a vaginal spermicide be used.

These allowed methods of contraception have a failure rate of less than 1% per year but are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

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### 11.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

**Phase III-IV liver chemistry stopping and increased monitoring criteria** have been designed to assure subject safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).

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

#### Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
<b>ALT-absolute</b>	ALT $\geq$ 8xULN
<b>ALT Increase</b>	ALT $\geq$ 5xULN but <8xULN persists for $\geq$ 2 weeks ALT $\geq$ 3xULN but <5xULN persists for $\geq$ 4 weeks
<b>Bilirubin<sup>1, 2</sup></b>	ALT $\geq$ 3xULN <b>and</b> bilirubin $\geq$ 2xULN (>35% direct bilirubin)
<b>INR<sup>2</sup></b>	ALT $\geq$ 3xULN <b>and</b> INR>1.5, if INR measured
<b>Cannot Monitor</b>	ALT $\geq$ 5xULN but <8xULN and cannot be monitored weekly for $\geq$ 2 weeks ALT $\geq$ 3xULN but <5xULN and cannot be monitored weekly for $\geq$ 4 weeks
<b>Symptomatic<sup>3</sup></b>	ALT $\geq$ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> <li>Immediately discontinue study treatment</li> <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 subject until liver chemistries resolve, stabilize, or return to within baseline (see <b>MONITORING</b> below)</li> <li><b>Do not restart</b> subject with study treatment unless allowed per protocol and GSK Medical Governance approval <b>is granted</b> (refer to</li> </ul>	<ul style="list-style-type: none"> <li>Viral hepatitis serology<sup>4</sup></li> <li>Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody<sup>5</sup>.</li> <li>Blood sample for pharmacokinetic (PK) analysis, obtained within 3 half lives (15 days) of last dose<sup>6</sup></li> <li>Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</li> <li>Fractionate bilirubin, if total</li> </ul>

	bilirubin $\geq$ 2xULN.
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<p><a href="#">Appendix 5</a>)</p> <ul style="list-style-type: none"> <li>• <b>If restart is not granted</b>, permanently discontinue study treatment and continue subject in the study for any protocol specified follow up assessments</li> <li>• Re-challenge is not allowed.</li> </ul> <p><b>MONITORING:</b>  <b><u>For bilirubin or INR criteria:</u></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 hrs</b></li> <li>• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline</li> <li>• A specialist or hepatology consultation is recommended</li> </ul> <p><b><u>For All other criteria:</u></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> </ul> <p>Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline</p>	<ul style="list-style-type: none"> <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, other over the counter medications.</li> <li>• Record alcohol use on the liver event alcohol intake case report form</li> </ul> <p><b><u>For bilirubin or INR criteria:</u></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 pressure liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [<a href="#">James</a>, 2009]). <b>NOTE: not required in China</b></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 subject if ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT  $\geq$  3xULN **and** bilirubin  $\geq$  2xULN (>35% direct bilirubin) or ALT  $\geq$  3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding**

**studies of hepatic impairment or cirrhosis**); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

### Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
<p>ALT <math>\geq</math>5xULN and &lt;8xULN <b>and</b> bilirubin &lt;2xULN <b>without</b> symptoms believed to be related to liver injury or hypersensitivity, <b>and</b> who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT <math>\geq</math>3xULN and &lt;5xULN <b>and</b> bilirubin &lt;2xULN <b>without</b> symptoms believed to be related to liver injury or hypersensitivity, <b>and</b> who can be monitored weekly for 4 weeks.</p>	<ul style="list-style-type: none"> <li>• Notify the GSK medical monitor <b>within 24 hours</b> of learning of the abnormality to discuss subject safety.</li> <li>• Subject can continue study treatment</li> <li>• Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline</li> <li>• If at any time subject meets the liver chemistry stopping criteria, proceed as described above</li> <li>• If ALT decreases from ALT <math>\geq</math>5xULN and &lt;8xULN to <math>\geq</math>3xULN but &lt;5xULN, continue to monitor liver chemistries weekly.</li> <li>• If, after 4 weeks of monitoring, ALT &lt;3xULN and bilirubin &lt;2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.</li> </ul>

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## 11.4. Appendix 4: Liver Safety Drug Restart Guidelines

If subject meets liver chemistry stopping criteria do not restart subject with study treatment unless:

GSK Medical Governance approval **is granted** (as described below),

Ethics and/or IRB approval is obtained, if required, and

Separate consent for treatment restart is signed by the subject

If GSK Medical Governance approval to restart the subject with study treatment **is not granted**, then the subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

### ***Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment***

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury) or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded.
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section [6.2.2](#) and [Appendix 5](#)

## **11.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events**

### **11.5.1. Definition of Adverse Events**

#### **Adverse Event Definition:**

- An AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

#### **Events meeting AE definition include:**

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

#### **Events NOT meeting definition of an AE include:**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 11.5.2. Definition of Serious Adverse Events

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, etc).

**Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:**

#### **Results in death**

##### **Is life-threatening**

NOTE:

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

#### **Requires hospitalization or prolongation of existing hospitalization**

NOTE:

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

#### **Results in disability/incapacity**

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza,



and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
<b>Is a congenital anomaly/birth defect</b>
<p><b>Other situations:</b></p> <ul style="list-style-type: none"> <li>Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.</li> <li>Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse</li> </ul>
<p><b>Is associated with liver injury <u>and</u> impaired liver function defined as:</b></p> <ul style="list-style-type: none"> <li>ALT <math>\geq</math> 3xULN and total bilirubin* <math>\geq</math> 2xULN (&gt;35% direct), <b>or</b></li> <li>ALT <math>\geq</math> 3xULN and INR** <math>&gt;</math> 1.5.</li> </ul> <p>* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT <math>\geq</math> 3xULN and total bilirubin <math>\geq</math> 2xULN, then the event is still to be reported as an SAE.</p> <p>** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.</p>

### 11.5.3. Recording of AEs and SAEs

<b>AEs and SAE Recording:</b>
<ul style="list-style-type: none"> <li>When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.</li> <li>The investigator will then record all relevant information regarding an AE/SAE in the CRF</li> <li>It is <b>not</b> acceptable for the investigator to send photocopies of the subject'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 instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.</li> </ul>

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

#### 11.5.4. Evaluating AEs and SAEs

##### Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

##### Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.

- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

#### Follow-up of AEs and SAEs

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

#### 11.5.5. Reporting of SAEs to GSK

##### SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor or the SAE coordinator
- Site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool (e.g.,

InForm system) will be taken off-line to prevent the entry of new data or changes to existing data

- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

## **11.6. Appendix 6: Collection of Pregnancy Information**

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, 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 5](#). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

### **Any female subject who becomes pregnant while participating**

- will discontinue study medication

## **11.7. Appendix 7: Electronic Health Record Ancillary Study**

### **11.7.1. Introduction**

#### **11.7.1.1. Background**

Clinical researchers and policy makers want to move towards embedding clinical trials directly within health care delivery systems in order to increase the relevance, speed, and efficiency of clinical research [Richesson, 2013]. The assumption is that the capabilities offered by Electronic Health Records (EHRs), along with concurrent changes in health care organization and delivery, and the development of a learning health system will transform the way clinical research is conducted [Etheredge, 2007; Greene 2007].

In 2011, the National Heart, Lung, and Blood Institute (NHLBI) convened the NHLBI Working Group on Electronic Health Records: Research Priorities to Improve Cardiopulmonary Health in Clinical Practice. As part of their mission, this working group identified key research, policy, and training priorities [Curtis, 2014]. A key research priority was to leverage EHR tools to facilitate the efficient implementation of randomized clinical trials. Specific areas highlighted for increased efficiency included efficient data collection and outcome surveillance and confirmation.

#### **11.7.1.2. Literature Review**

Electronic Health Records were primarily designed to document patient care and facilitate billing and reimbursement. The large amount of electronic data that are captured may also facilitate clinical research and public health surveillance.<sup>5</sup> Despite the complexity of EHR data, national networks have begun to use these data to improve public health and generate real-world evidence [Toh, 2012]. The Patient Centered Outcomes Research network (PCORnet) (pcornet.org) is a research network that is currently being designed to support observational comparative effectiveness research and clinical trials that are embedded in clinical care settings [Fleurence, 2014]. Similarly, the NIH Health Care Systems Research Collaboratory (nihcollaboratory.org) is creating infrastructure to improve the conduct of embedded clinical trials. One ongoing NIH Collaboratory trial is the Time to Reduce Mortality in End-Stage Renal Disease study (TiME) (clinicaltrials.gov identifier: NCT02019225). TiME is a large cluster-randomized, pragmatic trial that will evaluate the effects of systematic implementation of hemodialysis sessions of at least four hours versus usual hemodialysis care. The trial involves data acquisition from EHR systems through a partnership between academic investigators and two health care provider organizations with different electronic data systems. There are several other recent examples of clinical trials that were embedded in health care delivery systems [Gulliford, 2014; van Staa, 2014]. For instance, one recent study evaluated the use of an electronic decision support tool to improve risk factor control (i.e., blood pressure and cholesterol) following a cerebrovascular event with outcome data collected from the EHR [Dregan, 2014]. While the specific intervention was not shown to be efficacious, data acquisition via EHR sources was robust and implemented at a low cost.

### 11.7.1.3. Ancillary Study Rationale

Despite these earlier studies demonstrating the potential opportunities with EHR-based data acquisition, our understanding of how EHR-based platforms might increase the efficiency of data collection, outcome surveillance, and confirmation in an integrated manner is unknown. EHRs are inherently heterogeneous, with each implementation different from the next. The barriers to using EHR-generated lists of patients to facilitate trial enrolment, the fitness of EHR data for populating baseline characteristics in an electronic case report form (eCRF) and the use of EHR data to find events of interest during trial follow-up are not well characterized.

EHR systems contain a wealth of clinical data about patients who are connected to the health care delivery system and may be eligible for enrollment in a clinical trial. Anecdotal reports suggest that identification of potential patients using the EHR increases the number of patients to be screened but may not consistently translate to an increased number of patients enrolled. Causes are likely multi-factorial and may include the translatability of inclusion and exclusion criteria to structured clinical data, the algorithm used to identify potential patients, institutional restrictions regarding unsolicited patient contact, and others. There is a need to empirically assess the barriers to using an EHR-generated list of patients to facilitate trial enrollment.

Structured data captured in the EHR may be similar to data elements specified in baseline patient characteristics in the eCRF, yet EHR data are collected primarily to support clinical care and reimbursement needs. Their fitness for use as source data for selected data elements of the baseline patient characteristics in the eCRF has not been established.

During routine trial follow-up, study coordinators typically gather information from various sources including direct patient contact and medical records of the enrolling institution and outside facilities to document events for study participants. Evidence from the West of Scotland Coronary Prevention Study suggests that cardiovascular endpoints can be ascertained from routinely recorded EHR-type data, but classification was imperfect [Barry, 2013]. There is a need to specifically assess the utility of EHR data acquisition for follow-up events across multiple health systems.

In summary, the EHR is a rich source of clinical data, but is designed specifically to support clinical care delivery and reimbursement needs. The assumption that EHR data are fit for use in high-quality clinical research has not been rigorously evaluated. To provide evidence to address this knowledge gap, GlaxoSmithKline (GSK) and Duke Clinical Research Institute (DCRI) are committed to conducting an exploratory EHR Ancillary Study embedded within a large pragmatic clinical trial at selected study sites. The overarching goal is to further our understanding of how EHR data can be organized into a query-able format to facilitate a more efficient, reliable, and cost-effective research process. The proposed empirical work is exploratory in nature and both qualitative and quantitative.

## **11.7.2. Ancillary Study OBJECTIVES**

### **11.7.2.1. Primary Objectives**

#### **Objective 1: Assess the barriers to using an EHR-generated list of patients to facilitate trial enrollment.**

Through site study coordinator surveys, workflow assessment, analysis of electronic screening logs, comparisons of enrolled patients with patients identified via algorithm, this retrospective objective will describe the screening “funnel” and identify factors responsible for narrowing the funnel from the pool of potentially eligible patients to those enrolled in the clinical trial. Barriers for using EHR systems for this purpose will be assessed at the site level and common cross-site themes will be identified.

#### **Objective 2: Evaluate the fitness of EHR data for use in populating the baseline characteristics in the eCRF**

After study completion and within selected data areas (e.g., demographics, medical history, concomitant medications), the level of agreement between data extracted from the EHR and data documented on the baseline eCRF (reference standard) will be evaluated. Additionally the performance of algorithms developed to identify comorbidities and other clinical concepts will be assessed at the site level and aggregated, where appropriate.

#### **Objective 3: Explore the use of EHR data to find events of interest during trial follow-up**

Case-finding algorithms will be developed for select specified endpoints (i.e., myocardial infarction, stroke, unstable angina, heart failure as outlined in the main study protocol), run during the conduct of the trial, and used to identify potential cases for follow-up by the study coordinator. The site study coordinator will record the dispensation of each potential case so that reconciliation can occur between eCRF documented events and EHR-generated potential events. Safety event reporting will proceed as outlined in the main study protocol (Main Protocol Section 6.2). At the conclusion of the study, the yield of case-finding algorithms will be evaluated along with the performance of EHR-based algorithms with eCRF-reported as well as adjudicated eCRF-reported events (reference standard).

### **11.7.2.2. Secondary Objective**

As a secondary objective, an assessment of the general utility and feasibility of EHR-based outcome acquisition from the coordinator perspective through surveys and standardized workflow assessments will be conducted.

## **11.7.3. Ancillary Study design**

### **11.7.3.1. Study Design**

The ancillary study will occur in the context of the HARMONY-Outcomes trial, a randomised, double blind, parallel-group, placebo-masked, controlled study to evaluate



the effect of albiglutide on cardiovascular events in patients with Type 2 diabetes. Albiglutide will be administered subcutaneously once weekly in a population of patients with Type 2 diabetes and a previous history of cardiovascular disease and who do not have optimal glycaemic control). The duration of the ancillary study will mirror that of the HARMONY-Outcomes trial. The number of sites that will participate in the ancillary study depends upon the outcome of the site EHR capabilities assessment described in Section 11.7.3.2 (Site Selection) below. Five study sites recruiting 12-15 subjects each would enable a descriptive assessment of Objectives 1 and 2, whilst, if feasible, 500-1000 subjects at EHR-enabled sites would permit greater precision to be achieved in the assessment of Objective 3.

#### **11.7.3.2. Site Selection**

Sites from the main trial will be selected to participate. As part of the overall site selection process for the main trial, potential sites complete a feasibility survey to gauge their suitability for participation in the HARMONY-Outcomes trial. In addition to questions regarding experience with long-term outcome trials in general and specific features of the planned trial, the feasibility survey includes questions about site readiness for an EHR-facilitated trial. Specific topics include:

- Existence of an EHR system;
- Current use of EHR to screen for potential study participants;
- Types of information currently contained in EHR (inpatient visits, outpatient visits, laboratory results, medications)
- Prior participation in a study that used EHR data for patient screening, follow-up, and/or data collection; and
- Local EHR support to assist with research studies.

Sites who meet minimum qualifications based on this survey (respond affirmatively regarding the existence of an EHR system and local EHR support to assist with research studies), and who have confirmed an interest in participating in the ancillary study will be approached for a more in-depth assessment of capabilities. Specific topics include:

- Current capability to extract EHR-type data from a data warehouse;
- Data domains currently included in the data warehouse (e.g., demographics, vital signs, diagnoses, procedures, medications prescribed, laboratory tests, and death);
- Coding terminologies used for each domain of data;
- Institutional processes and policies for using EHR-type data for clinical research;
- Institutional experience extracting, transforming, and loading warehouse data into a research DataMart that conforms with standardized specifications; and

- Familiarity with or participation in distributed research networks.

Subsequent structured discussions with individual sites may be necessary to explore capabilities and suitability for the ancillary study. For example, engagement of the health system's Information Technology (IT) personnel will be essential but is challenging to gauge in a written survey. Key site selection criteria include:

- Fully implemented EHR system
- Access to an enterprise data warehouse or clinical data repository that stores structured data from the EHR and is updated at least weekly.
- Availability of necessary data
- Engagement of health system IT and analytical personnel

The advantage of a multi-stage, rapid assessment of capabilities is that it allows for a relatively short feasibility survey that can be completed reliably by a study coordinator. Detailed technical questions are reserved for the individuals who provide EHR support for research studies.

#### **11.7.3.3. Data Flows**

The methods for data extraction and capture will require a partnership between study site teams (site principal investigator, site study coordinator, and site technical support), GSK, and the DCRI Data Management Team.

The study will utilize PopMedNet, a software application that enables the creation, operation, and governance of research networks. It allows partners to maintain physical and operational control over their data while allowing authorized users to send queries to the data. PopMedNet consists of two layers: a security layer where access controls and permissions are established and a layer of virtual pipes through which questions are sent from requestor to responder. The PopMedNet software consists of a web-based "network portal" and a DataMart Client application that is installed at each site. PopMedNet employs a "publish-and-subscribe" architecture that does not require a hole through an institutional firewall, but rather allows institutions to pull a query behind the firewall for manual or automated execution.

In research networks with a common data model, PopMedNet is used to distribute executable code that institutions can choose to pull behind their firewall, run against the data in that appropriate format, and return results to the requestor. Security documentation will be provided to all participating sites.

The data flow for this ancillary study will be as follows:

- a) The study site's EHR system will not be changed and will continue to operate as implemented. Data from the thousands of tables in the EHR will be integrated on a nightly basis into a data warehouse that supports research needs (the term EHR

- is used to mean the system that collects, displays, and stores transactional health care data).
- b) With guidance from the DCRI Data Management Team, the study site's technical team will extract, transform, and load data from the enterprise data warehouse (or clinical data repository) to a Cohort DataMart according to the specifications of the common data model. A common data model standardizes the definition, content and format of data across sites to enable efficient, cross-site querying. The Cohort DataMart will be refreshed from the existing Data Warehouse on a biweekly basis. The Cohort DataMart includes Protected Health Information (PHI) for a broadly defined cohort of potential study participants and will remain behind institutional firewalls.
  - c) Data from Pre-Screening logs completed as part of the main study will be captured in a database stored in the same area as the Cohort DataMart to facilitate characterization of the screening funnel. Data from the pre-screening log will enable comparisons of characteristics of potential participants identified via algorithm with patients screened and enrolled.
  - d) When a participant is randomized into the study, the study coordinator will enter key subject identifiers (the main trial identifier (ID), Medical Record Number (MRN) equivalent, study randomization date) into the Key Identifier spread sheet.
  - e) Via PopMedNet, the DCRI Data Management Team will distribute code that extracts data for randomized participants from the Cohort DataMart into the Study DataMart using the Key Identifier table. Trial ID and randomization date from the Key Identifier table will be included in the Study DataMart. Data for randomized patients at each site will be returned to the DCRI via the HARMONY-Outcomes trial EHR Ancillary Study Query Portal.
  - f) Via PopMedNet, the DCRI will distribute executable code (e.g., SQL program) that will query the Study DataMart for potential study endpoints. [See Section [11.7.3.4.1b](#) for case-finding algorithm].
  - g) Potential cases (identified via case-finding algorithm) will be returned to the Study Coordinator who will record the dispensation of each potential case in the Case-finding Dispensation Log stored in the Study DataMart (i.e., recorded in the eCRF/not recorded in the eCRF and reasons).
  - h) The Study DataMart containing randomized patient data will be transferred from each site to the DCRI on a regular basis (anticipated quarterly with specific frequency to be determined).
  - i) Required data elements from the main clinical trial dataset for EHR Ancillary Study sites will be transferred from GSK to the DCRI after the completion of the study. The DCRI will merge data elements from the main clinical trial dataset with Study DataMart data to create the EHR Ancillary Study Dataset.

#### **11.7.3.4. Study Procedures and Processes**

##### **11.7.3.4.1. DCRI**

###### **a) Establish broad definition of cohort**

A broad cohort identification algorithm will be developed based on selected inclusion criteria outlined in the main study protocol. Selected criteria for inclusion into the cohort include:

- Age > 40 years old
- Diagnosis of Type 2 diabetes, broadly defined by diagnosis codes and medications prescribed (See 4.4 for information about algorithms to be used.)
- Established cardiovascular disease (See Section 11.7.4.4 for information about algorithms to be used)

Participating sites will be required to run the “cohort algorithm” within their EHR systems to create the Cohort DataMart which will be used as a basis for Objective #1.

###### **b) Specify contents of the EHR Ancillary Study research DataMart**

EHR data are stored in many different ways. A common data model standardizes the definition, content and format of data across sites to enable a single standardized view that can be used for querying. Sites participating in this ancillary study will be required to transform their data into a common data model that will be designed to be intuitive and user-friendly. Investigators and analysts with prior experience using research data will not need additional skills or knowledge to use the common data model. The DCRI team will manage questions and issues that arise regarding transforming data into the CDM.

The EHR Ancillary Study Common Data format will be adapted from the Patient Centered Outcomes Research Network (PCORnet) Common Data Model (<http://pcornet.org/resource-center/pcornet-common-data-model/>) and may include the following data areas:

- Demographic
- Encounter
- Diagnosis
- Procedure
- Medications prescribed
- Laboratory results, selected

**c) Develop data characterization routines**

As previously described, participating sites will transform local data into the study common data model. The DCRI Data Management Team will develop and distribute code to query the content of tables formatted according to the common data model. The distributed code will generate aggregate output tables that help determine whether the data conform to specifications, maintain integrity across variables and across tables, and trend as expected over time. The data quality review and characterization process will help to ensure that the data meets reasonable standards for data transformation consistency and quality.

DCRI's team will evaluate the creation of the Cohort DataMart using standard programs distributed to each study site for execution behind institutional firewalls.

**d) Develop and distribute test queries**

A series of simple test queries will be developed and distributed to sites for execution against a simulated data set, structured according to the common data model. The test queries will help each site become familiar with PopMedNet and distributed querying without concern about querying against protected health information.

**e) Develop algorithms for analytic variables**

Algorithms to map EHR-based data in the Study DataMart to baseline characteristics and study endpoints in the EHR Ancillary Study dataset will be defined using diagnosis codes (ICD-9-CM and ICD-10-CM) and procedure codes (ICD-9-CM and ICD-10-PCS). Published algorithms will be used whenever possible. Examples of published algorithms utilized in the past include:

- CMS chronic condition categories: <https://www.ccwdata.org/web/guest/condition-categories>
- Quan, H., Sundararajan, V., Halfon, P., Fong, A., Burnand, B., Luthi, J. C., ... & Ghali, W. A. (2005). Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care*, 1130-1139. <http://www.ncbi.nlm.nih.gov/pubmed/16224307>
- Elixhauser, A., Steiner, C., Harris, D. R., & Coffey, R. M. (1998). Comorbidity measures for use with administrative data. *Medical Care*, 36(1), 8-27. <http://www.ncbi.nlm.nih.gov/pubmed/9431328>

These algorithms will be updated as necessary to account for coding changes since publication. And, if not provided, mapping of diagnosis codes from ICD-9-CM to ICD-10-CM and mapping of procedure codes from ICD-9-CM to ICD-10-PCS will be done using the general equivalence mappings provided by Centers for Medicare & Medicaid Services (CMS):

- Diagnosis code crosswalk: <http://www.cms.gov/Medicare/Coding/ICD10/2014-ICD-10-CM-and-GEMs.html>

- Procedure code crosswalk: <http://www.cms.gov/Medicare/Coding/ICD10/2014-ICD-10-PCS.html>

Algorithms used to identify specific medications dispensed will be defined using different drug identification coding systems in use by study sites. These systems could include:

- NDC codes [from RxNav, a browser for drug information available from the U.S. National Library of Medicine]
- DIN codes [from Health Canada drug product database]
- ATC codes [from WHO Collaborating Centre for Drug Statistics Methodology]

#### **11.7.3.4.2. Sites**

Participating study sites will:

- Extract, transform, and load (ETL) data into a physical instance of an adapted PCORnet Common Data Model. Sites will document the mapping from the EHR to the Common Data Model.
- Install PopMedNet
- Refresh the Cohort DataMart on a biweekly basis
- Execute data characterization and test queries after each refresh and on an as-needed basis.

Site study coordinators will be required to complete pre-screening logs on all potential study participants meeting minimum eligibility requirements (age >40, Type 2 diabetes, established cardiovascular disease) identified via any mechanism (i.e., reviewing lists of scheduled office patients, reviewing lists of recently discharged diabetes patients, EHR-facilitated algorithm). Pre-screening logs will capture the following information:

- Pre-screening number
- Pre-screening date
- Inclusion criteria not met
- Exclusion criteria met
- Other criteria

Site study coordinators will complete a screening survey which will describe the site's current process for screening. A description of screening barriers will be included.

## 11.7.4. DATA ANALYSIS

### 11.7.4.1. Sample Size Expectations

The objectives of this ancillary study are exploratory (not confirmatory) in nature and not intended to be sufficiently powered to confirm a pre-determined level of sensitivity and specificity. The number of sites and subjects that will participate in the ancillary study depends upon the outcome of the site EHR capabilities assessment described in Section 11.7.3.2 (Site Selection). Five study sites recruiting 12-15 subjects each would enable a descriptive assessment of Objectives 1 and 2, whilst, if feasible, 500-1000 subjects at EHR-enabled sites would permit greater precision to be achieved in the assessment of Objective 3.

### 11.7.4.2. Objective 1: Assess the Barriers to Using as EHR-Generated List of Patients to Facilitate Trial Enrollment

Because any survey administered for this objective will be a site-level survey, analysis of the survey data will be performed across all sites. For quantities of interest, frequencies with percentages for categorical measures and means with standard deviations for continuous measures will be presented.

### 11.7.4.3. General Analytic Approach for Objective 1 and Objective 2

The goals of both Objective 2 and Objective 3 involve evaluating the performance of algorithms that map EHR-based data into concepts present in the clinical trial dataset. The actual measures recorded in the clinical trial dataset will be considered the reference standard against which these algorithm-based measures are compared.

**Table 3 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Categorical variables**

	Reference standard (Clinical trial data)	
	Condition present	Condition absent
New measure (EHR Ancillary Study data)		
Condition present	True positive (TP)	False positive (FP)
Condition absent	False negative (FN)	True negative (TN)

For categorical variables, estimated performance metrics will be based on the 2x2 cross-tabulation of values in the EHR Ancillary Study dataset with values in the clinical trial dataset (Table 3) and include:

$$\text{Overall agreement} = (TP + TN) / (TP + FP + FN + TN)$$

$$\text{Sensitivity} = TP / (TP + FN)$$

$$\text{Specificity} = TN / (FP + TN)$$

Positive predictive value =  $TP / (TP + FP)$

Negative predictive value =  $TN / (FN + TN)$

Accuracy or efficiency =  $(TP + TN) / (TP + TN + FP + FN)$

For dichotomous measures, each of these proportions is immediately calculable. For measures having more than two levels, multiple dichotomous measures will be created in order to calculate these proportions. Confidence intervals (95%) will be reported around these quantities. (See [Table 4](#) as an example).

**Table 4 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Categorical variables**

Measure	Overall agreement (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Measure 1	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
Measure 2	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)	xx.x (xx.x – xx.x)
.....	.....	.....	.....	.....	.....

Reported on 0–100 scale

For continuous measures, bias will be calculated as the difference between values in the EHR Ancillary Study dataset and values in the clinical trial dataset. The mean and standard deviation of the bias along with a 95% confidence interval will be reported. In Bland-Altman analyses of agreement between continuous measures, the standard deviation of the bias is referred to as the precision, while the 95% confidence interval is referred to as the limit of agreement. (See [Table 5](#) as an example).

**Table 5 Overall performance of EHR-based algorithms for baseline characteristics, using clinical trial data as the reference standard / Continuous variables**

Measure	Bias	
	Mean (SD)	95% (CI)
Measure 1	xx.x	xx.x
Measure 2	xx.x	xx.x
.....	.....	.....

Due to the nature of EHR data, it is expected that there will be systematic differences between sites with respect to coding of clinical concepts. All performance metrics will therefore initially be calculated by site. These site-specific results may be best reported graphically.



There is also interest in an assessment of algorithm performance across all sites. Hierarchical models will be used to combine data from all sites and estimate performance at the “average” site. To estimate proportions (e.g. for overall agreement, sensitivity, specificity, etc. associated with categorical measures), models will be specified as:

$$\begin{aligned} \text{logit}(E(y)) &= \beta_0 + \gamma_{0,j} \\ \gamma_{0,j} &\sim N(0, s^2) \end{aligned}$$

where sites are indexed by  $j$ . The value of the proportion at the average site—when  $\gamma_0=0$ —is  $[1 + \exp(-\beta_0)]^{-1}$ . Patients included in the estimation of each model vary by performance metric and reflect the definitions above. As an example, consider positive predictive value. To estimate the positive predictive value of an algorithm, only subjects with true positive value and false positive values will be included. True positives will be assigned  $Y=1$  and false positive will be assigned  $Y=0$ .

To estimate means (e.g. for bias associated with continuous variables), the model will be specified as:

$$\begin{aligned} E(y) &= \beta_0 + \gamma_{0,j} \\ \gamma_{0,j} &\sim N(0, s^2) \end{aligned}$$

The value of the mean at the average site is  $\beta_0$ .

For all models, we will assess site heterogeneity by testing if  $s^2=0$ .

#### **11.7.4.4. Objective 2: Evaluate the Fitness of EHR Data for Use in Populating the Baseline Characteristics in the eCRF**

Algorithms will be defined to map EHR-based data in the Study Data Mart to specific concepts in the EHR Ancillary Study dataset that parallel concepts in the clinical trial dataset. For Objective 2, the performance of algorithms used to identify baseline characteristics will be evaluated. The baseline characteristic measures recorded in the clinical trial dataset will be considered the reference standard against which these algorithm-based measures are compared.

#### **11.7.4.5. Objective 3: Explore the Use of EHR Data to Find Events of Interest During Trial Follow-up**

Algorithms will be defined to map EHR-based data in the Study Data Mart to specific concepts in the EHR Ancillary Study dataset that parallel concepts in the clinical trial dataset. For Objective 3, the performance of algorithms used to identify trial events will be evaluated. These algorithms will be evaluated against both the adjudicated events recorded in the clinical trial dataset and the identified potential events in the eCRF. For each event, estimates of sensitivity and positive predictive value (described in Section [11.7.4.3](#)) will be calculated and presented with 95% confidence intervals.

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