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24/09/2014
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Please see Study Procedures Manual for details regarding submission of back-up paper SAE CRF pages.

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number GLP110933

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

ADA	American Diabetes Association
ADDQoL	Audit of Diabetes Dependent Quality of Life
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-IA-2	Antibody to protein tyrosine phosphatase-like protein
Anti-GAD	Antibody to Glutamic Acid Decarboxylase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BLQ	Below level of quantification
β-hCG	β-human chorionic gonadotropin
BMI	Body mass index
CGM	Continuous glucose monitoring
CHMP	Committee for Medicinal Products for Human Use
CPK	Creatine phosphokinase
CV	Cardiovascular
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic keoacidosis
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidypeptidase-IV
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
GSK	GlaxoSmithKline
HA	Human albumin
HbA1c	Glycosylated haemoglobin A1c
HPLC	High performance liquid chromatography
IAA	Insulin autoantibody
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDAA1c	Insulin Dose Adjusted A1c
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
INR	International Normalised Ratio
IRB	Institutional Review Board
ITT	Intent to treat
LDH	Lactate dehydrogenase

IP	Investigational Product
IVRS	Interactive voice response system
LSLV	Last subject last visit
MAR	missing at random
MDRD	Modification of Diet in Renal Disease
MMTT	Mixed meal tolerance test
NAb	Neutralising antibody
NOT1DM	New-onset type 1 diabetes mellitus
PAC	Pancreatitis Adjudication Committee
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PGx	Pharmacogenetic
PK	Pharmacokinetic
QoL	Quality of Life
QTc	corrected QT interval
RBCF	Residual beta-cell function
RAP	Reporting and analysis plan
RNA	Ribonucleic acid
SAE	Serious Adverse Event
sc	Subcutaneous
SD	Standard deviation
SMPG	Self-monitored plasma glucose
SPM	Study Procedures Manual
SU	Sulphonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione
ULN	Upper limit of normal

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PROTOCOL SUMMARY

Rationale

Despite introduction of modern analogue insulins, and improved methods of delivery such as continuous subcutaneous insulin infusion using a pump, glucose control in patients with type 1 diabetes mellitus (T1DM) remains suboptimal, leading to an increased burden of complications of diabetes including blindness, renal failure and amputation. It is recognised that patients with preserved pancreatic β-cell function and hence endogenous insulin production, who require a lower overall dose of insulin replacement therapy, achieve better glycaemic control and experience a reduced burden of long term complications.

Glucagon-like peptide-1 receptor (GLP-1R) agonists stimulate insulin secretion in a glucose-dependent manner and suppress glucagon secretion, resulting in lower fasting plasma glucose and reduced postprandial glucose excursions with a low risk of hypoglycaemia. GLP-1R agonists also delay gastric emptying, increase satiety and are associated with modest weight reduction. These physiological effects of GLP-1 therapies may lead to an improvement in glycaemic control in subjects with T1DM.

Pre-clinical evidence from rodent models suggests that GLP-1R agonists may also preserve β-cell function. This study seeks to evaluate the effect of albiglutide, a GLP-1R agonist, on endogenous insulin production, (measured by stimulated C-peptide), exogenous insulin requirements, (as measured by total daily insulin dose per kg of body weight, and glycaemic variability over one year in subjects with T1DM and residual β-cell function. The results of this study will determine the next steps in the development of albiglutide as a novel therapy for subjects with T1DM.

Objectives and Endpoints

Objective	Endpoint
Primary	
Determine the effect of albiglutide therapy versus placebo on endogenous insulin secretion over 52 weeks when added to standard of care in subjects with new onset type 1 diabetes mellitus (NOT1DM)	Primary Endpoint: Mean change from baseline in stimulated (from mixed meal tolerance test [MMTT]) 2 hour plasma C-peptide area under the curve (AUC) at Week 52 Secondary Endpoints linked to primary objective: Mean change from baseline in stimulated (from MMTT) 2 hour plasma C-peptide AUC at Week 16, 28 and Week 64 Maximum stimulated plasma C-peptide: the highest value at any time point during the 2 hour MMTT after the subject has ingested the mixed meal at Baseline, Week 16, Week 28, Week 52 and Week 64

Objective	Endpoint
Secondary	
To assess the effect of albiglutide versus placebo on plasma glucagon concentration during a MMTT	Mean change from baseline in plasma glucagon AUC (from MMTT) at Week 16, 28, 52 and Week 64
Determine the percentage of subjects meeting the definition of a responder (defined as having HbA1c ≤ 7.0% and mean daily insulin use < 0.5 units/kg/day) and the percentage of subjects achieving partial remission status (i.e., defined as subjects with Insulin Dose Adjusted A1c (IDAA1C) ≤ 9.0)	Percent of responders (defined as subjects with HbA1c < 7.0% and insulin dose < 0.5 units/kg/day) at Weeks 4, 8, 16, 28, 40, 52 and 64 Percent of subjects achieving insulin dose-adjusted haemoglobin A1c (IDAA1C) ≤ 9.0 at Weeks 4, 8, 16, 28, 40, 52 and 64
To assess glycaemic control in both treatment groups as measured by HbA1c	Change from Baseline in HbA1c at Week 52 and HbA1c over time (i.e., at Weeks 4, 8, 16, 28, 40, 52 and 64
Determine differences in total daily insulin dose between treatment groups	Change from baseline in mean daily insulin use over the 3 days preceding the visit at Weeks 4, 8, 16, 28, 40, 52 and 64. The mean daily insulin use value will be calculated, in units/kg/day, as the mean of the values of the total amount of insulin used per day on each of the 3 consecutive days
Determine any differences in significant hypoglycaemia (i.e., events with plasma glucose < 3.9 mmol/L and/or requiring third party intervention) between treatment groups	Number of events of hypoglycaemia with confirmed self plasma glucose monitoring < 3.9 mmol/L and/or requiring third party intervention (i.e., severe, documented symptomatic and asymptomatic hypoglycaemic events – see Section 6.4.2) occurring > Week 24 and ≤ Week 52
Compare glycaemic variability between treatment groups, as measured by 72-hour continuous glucose monitoring (CGM) and 7 point glucose profile	Time spent with a plasma glucose <3.9 mmol/L, between 3.9 and 10.0 mmol/L, and >10.0 mmol/L, respectively as performed by 72-hour CGM at Baseline, Week 28 and Week 52 Number and magnitude of hypoglycaemic (<3.9 mmol/L) and hyperglycaemic excursions (> 10.0 mmol/L) from the 7 point glucose profile at Baseline, Week 28 and Week 52
Determine the effect of albiglutide on body weight	Change from Baseline in body weight (kg) at Week 52 and Weight over time (i.e., at Weeks 2, 4, 6, 8, 16, 28, 40, 52 and 64)
Assess the safety and tolerability of albiglutide in subjects with NOT1DM	Incidence of hypoglycaemia (in total and by each category as defined by ADA criteria (see Section 6.4.2) overall and in 3 monthly intervals (i.e., from Baseline to Week 12, >Week 12 to

Objective	Endpoint
	≤Week 24, >Week 24 to ≤Week 36, >Week 36 to ≤Week 52, >Week 52 to ≤Week 64 Incidence of hypoglycaemia with plasma glucose <3.1 mmol/L (< 56mg/dL) regardless of symptoms) Incidence of daytime hypoglycaemia (in total and by ADA category) (defined as hypoglycaemic episodes with an onset between 06:00 h and 00:00 h (inclusive) and nocturnal hypoglycaemia (in total and by category) defined as hypoglycaemic episodes with an onset between 00:01 h and 05:59 h (inclusive) will be determined Adverse events and serious adverse events Other adverse events of special interest (AESI) (for example, cardiovascular, gastrointestinal, pancreatitis, malignancies (including pancreatic cancer and thyroid cancer), injection site reaction, liver events, potential systemic allergic reactions, atrial fibrillation/flutter, pneumonia, diabetic ketoacidosis [DKA i.e., ketonuria/ketonaemia, hyperglycaemia and acidaemia]) Assessment of clinical laboratory tests (haematology, biochemistry, urinalysis) Assessment of vital signs measurements, 12-lead electrocardiograms (ECGs) and physical examinations Immunogenicity (i.e., percentage of subjects developing anti-albiglutide antibodies and characterisation of anti-albiglutide antibodies)
To evaluate the albiglutide PK profile in subjects with NOT1DM	Population estimates of PK parameters (e.g., apparent clearance [CL/F], apparent volume of distribution [V/F], first-order absorption rate constant [K_a]), associated inter-subject variability and residual error Covariates and covariate effects on subject PK Population estimates of PD parameters (e.g., Emax, EC_{50}), associated inter-subject variability

Objective	Endpoint
	and residual error if permitted by the data
Exploratory	
Assess the effect of albiglutide on T1DM-associated auto-antibodies (antibody to glutamic acid decarboxylase (anti-GAD) antibody to protein tyrosine phosphatase-like protein (anti-IA-2) and insulin autoantibody (IAA))	Change from baseline in anti-GAD, anti-IA-2 and IAA antibody titres at Week 4, Week 16, Week 28, Week 40, Week 52 and Week 64
Explore whether urinary C-peptide could be used in future phase III studies as an alternative to plasma C-pepide AUC from mixed meal testing as a measure of endogenous insulin secretion	Correlation of urinary C-peptide 120 minute after a mixed meal (urinary creatinine corrected) with MMTT plasma C-peptide AUC assessed at Baseline, Week 16, Week 28, week 52 and Week 64
Evaluate the PK and PD (PK/PD) relationship between plasma albiglutide concentration and measures of glycaemic control (e.g., C-peptide, insulin use, HbA1c, etc) and other potential efficacy, tolerability (e.g., nausea and vomiting) and safety endpoints as data permit	Graphical or model-based exploration of PK/PD relationships between albiglutide exposure (e.g., steady state AUC) and selected PD endpoints if appropriate and permitted by the data
Assess the effect of albiglutide on biomarkers associated with autoimmune pathology over 52 weeks in subjects with NOT1DM	A decision on whether to analyse biomarker samples will be made after review of efficacy endpoints at the end of the study. Exploratory biomarkers may include CD8-positive antigen-specific T-cells and biomarkers for β-cell death.
Assess the effect of albiglutide on diabetes-related quality of life as measured by the Audit of Diabetes Dependent Quality of Life Questionnaire (ADDQoL).	Change from baseline in ADDQoL global and domain scores and overview item scores at Week 52.
Assess the effect of albiglutide on β-cell function in the context of the prevailing glucose response to the MMTT	β-cell function, expressed as an insulin secretion parameter, will be estimated by modelling glucose and c-peptide concentrations. The modelling process will include, but is not limited to, the deconvolution of C-peptide data in the context of the prevailing glucose response to the meal

Study Design

This is a Phase II, randomised, double-blind, parallel group, placebo controlled, multicentre study of 52 weeks treatment duration in subjects with NOT1DM.

Approximately 68 eligible subjects will be randomised in a 3:1 ratio such that:

- 51 subjects receive albiglutide 30 mg once weekly (with increase to 50 mg once weekly at Week 6 if the 30 mg dose is tolerated) added-on to insulin therapy

- 17 subjects receive placebo once weekly added-on to insulin therapy

Blinded reduction of randomised study medication to the 30 mg once weekly dose may occur in the event of GI intolerability (i.e., nausea, vomiting or diarrhoea) after discussion between the investigator and medical monitor.

During the study, subjects will perform self monitored plasma glucose monitoring at least 4 times daily and adjust their basal and meal-time insulin requirements according to protocol-defined algorithm/guidance.

The total duration of a subject's participation will be approximately 72 weeks (up to 8 weeks of Screening, 52 weeks of treatment and 12 weeks of Post-treatment Follow-up).

Study Assessments

Efficacy Assessments

Mixed meal tolerance test (including urinary C-peptide), 72-hour continuous glucose monitoring, 7 point glucose profile, daily insulin usage, HbA1c, body weight, hypoglycaemia events, Audit of Diabetes Dependent Quality of Life (AddQoL) questionnaire

Safety assessments

Hypoglycaemia events, AE/SAEs (including AEs of special interest including DKA), pregnancy, clinical laboratory tests, immunogenicity, vital signs, 12-lead ECGs and physical examinations

1. INTRODUCTION

1.1. Background

Epidemiology of Type 1 diabetes mellitus (T1DM)

Diabetes mellitus (DM) is a metabolic disorder characterised by chronic hyperglycaemia due to deficiencies in production of or response to the hormone insulin. Approximately 382 million people have DM globally [IDF Diabetes Atlas, 2013]. A classification system developed by an international expert committee working under the sponsorship of the American Diabetes Association (ADA) recognises 4 types of DM: type 1 (T1DM; previously labelled Insulin Dependent Diabetes Mellitus or IDDM); type 2 (T2DM, the most common category, typically characterised by insulin resistance with relative insulin deficiency); gestational diabetes; and a final category that includes multiple specific but less common types of DM ([American Diabetes Association, 2014]. Patients with T1DM represent approximately 5% to 10% of all patients with DM.

T1DM is characterised by an absolute deficiency of insulin. The disease is classified in two subtypes: type 1a which includes the common, immune-mediated forms of the disease; and type 1b which includes non-immune forms [Concannon, 2009]. Approximately 85-90% of patients with T1DM have evidence of autoimmunity based on the presence of antibodies to islet cells, GAD, IA-2, IA-2β, and/or insulin. Patients with T1DM who lack evidence of autoimmunity are considered to have idiopathic T1DM, (type 1b).

Pathophysiology of autoimmune T1DM

Type 1a diabetes is caused by the autoimmune destruction of pancreatic β cells, the only cells in the body that produce insulin. Insulin-producing pancreatic β cells are specifically targeted and progressively destroyed by activated, autoreactive CD4+ and CD8+ T effector cells [Ryden, 2007]. This autoimmune attack leads to the progressive loss of β-cell function and endogenous insulin secretion culminating in an absolute dependence on exogenous insulin replacement therapy. T1DM is characterised by both increased background levels of glucagon and a paradoxical rise in glucagon levels in response to an oral glucose challenge [Kramer, 2013]. Both of these factors are likely to contribute to β-cell stress and may therefore accelerate the decline in β-cell function seen in new onset T1DM (NOT1DM).

The events triggering the development of an autoimmune attack on the β-cell are unclear. T1DM occurs most often in children, adolescents and young adults, but can present at any age. Although T1DM aggregates in some families, it does not segregate with any clear mode of inheritance reflecting a complex interaction between environment factors (such as viral infection) and inheritance in determining individual risk of developing T1DM [Van Belle, 2011; Coppieters, 2011].

Clinical symptoms of T1DM do not develop until a significant portion of the β cell mass has been destroyed or compromised as a result of the autoimmune process [Tsai, 2006]. It is estimated that only 10-20% of β-cells are still functioning at the time of clinical

diagnosis [Knip, 2002] and β-cell function continues to decline after diagnosis. β-cell function at the time of diagnosis is directly related to age, with younger patients tending to have less β-cell function at the time of diagnosis than older patients [Tsai, 2006; Bruno, 2005; Palmer, 2004; Porsen, 2007]. The rate of progression from normo-glycaemia, through pre-clinical impairment of glucose handling to insulin dependence is variable. Indeed, even 1-5 years after diagnosis, about 50% of T1DM show clinically meaningful β-cell function [Palmer, 2009].

Unmet need in T1DM

There are currently no curative treatments for T1DM. The focus of existing treatment is on regulating blood glucose levels using exogenous insulin and a controlled diet. Even though insulin replacement therapy and other advances in the management of T1DM (including insulin pumps and continuous glucose monitoring) have improved the prognosis and quality of life of patients with T1DM, their mortality is still approximately 2- to 10-fold higher than in the background population [Soedamah-Muthi, 2006].

Because of the lack of endogenous insulin production in T1DM, blood glucose levels are not regulated in a normal manner, and chronic hyperglycaemia and extreme fluctuations in glucose levels can occur. The resulting short term complications can include diabetic ketoacidosis (DKA) and hyperglycaemic coma and hypoglycaemia associated with insulin replacement therapy. In the long term suboptimal glycaemic control leads to an increased risk of microvascular complications involving the eyes, kidneys, and nerve tissue as well as macrovascular diseases such as atherosclerosis, coronary heart disease, stroke, and intermittent claudication. Patients with T1DM require long-term medical attention to limit and treat these complications.

For each individual patient with T1DM, the level of β-cell function is a critical factor in determining metabolic control and preventing complications [Palmer, 2004; Tsai, 2006]. It is well recognised in research and clinical practice that T1DM in patients with residual β cell function (RBCF) is more stable and easier to manage, with less hyperglycaemia (including less DKA), less hypoglycaemia (including fewer serious episodes), and a lower exogenous insulin requirement [Ostman, 2000; Madsbad, 1979; Home, 2003; Kolb, 2001; Palmer, 2004; Shima, 1977]. The Diabetes Control and Complications Trial (DCCT) and other studies have shown that patients with RBCF also have fewer long-term vascular complications, including retinopathy and nephropathy [Steffes, 2003; DCCT, 1998; Fukuda, 1988; Gonen, 1979; Grajwer, 1977; Johansson, 2000; Ludvigsson, 1977; Madsbad, 1980; Nakanishi, 1995; Sjoberg, 1991].

1.2. Rationale

GLP-1 receptor agonists as disease-modifying therapies in T1DM

A clear need exists therefore, for therapies that can either affect the underlying pathophysiology of T1DM and/or help patients with established disease improve glycaemic control and prevent complications. The incretin hormones, particularly glucagon-like peptide-1 receptor (GLP-1R) agonists, have the potential to do both.

GLP-1R agonists (e.g., albiglutide, exenatide, liraglutide and lixisenatide) are therapeutic agents for the treatment of type 2 diabetes mellitus (T2DM) that stimulate insulin secretion in a glucose-dependent manner and suppress glucagon secretion, resulting in lower fasting plasma glucose and reduced postprandial glucose excursions with a low risk of hypoglycaemia. GLP-1R agonists also delay gastric emptying, increase satiety and are associated with modest weight reduction. These physiological effects of GLP-1 therapies may lead to an improvement in glycaemic control in subjects with T1DM as well as in those with T2DM.

Preclinical studies in rodents, primarily in healthy and T2DM models, have shown that GLP-1R agonists stimulate transcription of genes important for glucose dependent insulin secretion and promote β-cell neogenesis [Gautier, 2005]. As β-cell function continues to decline following diagnosis of T1DM, these pre-clinical findings raise the possibility of using GLP-1R agonists early in the disease to help preserve the remaining β-cell function.

Pre-clinical evidence also suggests that GLP-1R agonists may positively impact on T cell function with respect to autoimmunity [Xue, 2008; Xue, 2010; Hadjiyanni, 2010; Bresson, 2009; Tooley, 2012]. It as yet unknown whether this will translate into a positive effect on cytotoxic T cell / T regulatory cell balance in humans, and hence have an effect on β-cell survival.

The therapeutic potential of GLP-1R agonists in T1DM is supported by a small study comparing liraglutide with placebo in patients with T1DM. After 4 weeks of liraglutide treatment at doses approved for treatment of adults with T2DM, patients with residual β-cell function had lower HbA1c, lower insulin doses and less time spent with blood glucose < 3.9 mmol/L (assessed by continuous glucose monitoring) compared with those on placebo [Kielgast, 2011]. A reduction in HbA1c and insulin dose was also seen in subjects on liraglutide without residual β-cell function with the reduction in insulin dose being positively correlated with β-cell function at baseline. There are also a number of small studies in subjects with established T1DM (with and without residual β-cell function) which have demonstrated glycaemic benefits of the GLP-1R agonist exenatide [Ramen, 2010; Sarkar, 2014; Ghazi, 2014; Kielgast, 2011]. However no studies assessing the effects of albiglutide in T1DM have been conducted to date.

The potential role of albiglutide in the treatment of T1DM

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 the amino terminus of recombinant human albumin. Albiglutide has been developed for the treatment of T2DM as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies. It has been approved by the EMA and the FDA as a treatment for T2DM. In a Phase III clinical trial, albiglutide in combination with insulin glargine was shown as generally safe and efficacious in controlling HbA_{1c} to target levels of <7.0% and <6.5%, in controlling fasting plasma glucose, favoured weight reduction and had positive effects on the need for hyperglycemia rescue compared to meal time insulin lispro [Study GLP108486, GlaxoSmithKline Document Number; 2011N126139_00].

This study seeks to evaluate the effect of albiglutide, compared to placebo, on endogenous insulin production and the preservation of β-cell function (as measured by stimulated C-peptide following a mixed meal), in insulin treated subjects with NOT1DM and residual β-cell function over one year. Albiglutide treatment will be added to a regimen of basal/meal-time insulin therapy. Insulin dose will be titrated according to a pre-defined algorithm with the aim of achieving equivalent glycaemic control in the 2 treatment arms. If albiglutide is able to preserve residual β-cell function this could lead to less hyperglycaemia (including less DKA), less hypoglycaemia (including fewer serious episodes), a lower exogenous insulin requirement and ultimately in the long-term, fewer vascular complications.

The results of this proof of concept study will determine the next steps in the development of albiglutide as a novel, and potentially disease-modifying therapeutic in subjects with T1DM.

1.3. Benefit:Risk Assessment

Albiglutide is in late stage development for T2DM and received regulatory approval for marketing on 27 Mar 2014 in the European Union and on 15 Apr 2014 in the United States. This current study is for a new indication; subjects with NOT1DM and is the first study of albiglutide for this indication. Therefore, the risk and benefit sections below have been derived from data and knowledge generated with albiglutide in subjects with T2DM.

Within subjects with T2DM, albiglutide has been evaluated in a comprehensive global programme of studies involving approximately 9000 patient-years of overall exposure to date (including over 4000 patient-years of exposure to albiglutide). There have been 8 well-controlled Phase III studies (including one study 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 programme has permitted a robust assessment of efficacy, safety, and tolerability in a representative T2DM population that spanned newly diagnosed subjects 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 Investigator's Brochure (IB) [GlaxoSmithKline Document Number; RM/2006/00602/07], any subsequent IB updates, and the product label. The following section outlines the risk assessment and mitigation strategy for this protocol.

1.3.1. Risk Assessment

Key risks (identified and potential) associated with the use of albiglutide, or the GLP-1R agonist class, as well as the mitigation strategy for key risks of clinical significance are provided in the table below. Please refer to the IB [GlaxoSmithKline Document Number; RM/2006/00602/07] and any subsequent IB updates, for a thorough summary of the nonclinical and clinical experience with albiglutide as well as the complete Guidance for the Investigator (IB Section 6). In addition, the risks associated with study participation, study procedures or comparators are also included in the table.

Identified/Potential/Other Risk of Clinical Significance	Data / Rationale for Risk	Mitigation Strategy
Investigational Product (IP): [albiglutide (GSK716155)]		
Pancreatitis [Identified risk]	In clinical trials in T2DM, acute pancreatitis has been reported in association with albiglutide and other GLP-1R agonists (Refer to Section 5.4.5.2 and Section 6 of the IB). Albiglutide has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk of pancreatitis.	Specific eligibility and withdrawal criteria (See Section 4) Risk communication via Guidance For Investigators (IB Section 6) and informed consent form for subjects
Gastrointestinal events [Identified risks]	Albiglutide has not been studied in patients with severe GI disease, including severe gastroparesis Use of albiglutide and other GLP-1R agonists may be associated with GI AEs e.g., diarrhoea, nausea, vomiting (Refer to Section 5.4.5.4 and Section 6 of the IB)..	Specific GI eligibility criteria (See Section 4) Risk communication via Guidance For Investigators (IB Section 6) and informed consent form for subjects Blinded reduction of randomised study medication in the event of GI intolerability (See Section 5.1.1)
Hypoglycaemia [identified risk]	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 (Refer to Section 5.4.5.1 and Section 6 of the IB).	Close monitoring for hypoglycaemia and need for intervention via frequent contact with subjects who will self-monitor plasma glucose (See Section 5.1.2). Risk communication via Guidance For Investigators (IB Section 6) and informed consent form for subject
Immunogenicity (e.g., clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, other immune related events) [identified risk]	In the Phase III programme in T2DM, approximately 5% of subjects developed anti-albiglutide antibodies but based on available clinical data, anti-albiglutide antibody formation is not expected to impact the overall safety or efficacy of albiglutide treatment (Refer to Section 5.6.1 of the IB). Although most patients with injection site reactions were antibody negative (approximately 85%), injection site reactions were reported more frequently for antibody positive (approximately 41%, than antibody negative patients, 14%). Hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III programme (Refer to Section 5.4.5.5 and Section 6 of the	Specific eligibility and withdrawal criteria (See Section 4) Risk communication to subject via informed consent form. Prohibited concomitant medication of immunoglobulins (see Section 5.6.2.)

Identified/Potential/Other Risk of Clinical Significance	Data / Rationale for Risk	Mitigation Strategy
	IB).	
Injection site reactions [Identified risk]	Albiglutide is given as a subcutaneous (sc) injection in the abdomen, thigh, or upper arm and may cause pain, swelling, redness, and/or infection at the injection site (Refer to Section 5.4.5.6 of the IB).	Risk communication via Guidance For Investigators (IB Section 6) and informed consent form for subject. . Patients will be advised that when injecting in the same region, to use a different injection site each week.
Other adverse reactions (e.g., pneumonia, atrial fibrillation/atrial flutter, appendicitis and hypersensitivity reactions) [identified risks]	In the Phase III programme for T2DM, other adverse reactions were observed with a cumulative incidence < 3% in studies up to 3 years in duration (Refer to Section 5.4.5.10, Section 5.4.5.11 and Section 6 of the IB)	Risk communication via Guidance For Investigators (IB Section 6) and informed consent form for subject Regular ECGs (see Section 6)
Thyroid C-cell tumours [potential risk]	This potential risk arises from non-clinical rodent studies where GLP-1R agonists have been associated with increases in serum calcitonin, thyroid C-cell focal hyperplasia, and C-cell tumours. The relevance of these observations to man is uncertain. In phase III studies of up to 3 years duration, albiglutide was not associated with clinically relevant increases in serum calcitonin (Refer to Section 5.4.5.3 and Section 6 of the IB)..	Subjects with a personal or family history of MTC or Multiple Endocrine Neoplasia syndrome type 2 are excluded (see Section 4). Risk communication via Guidance For Investigators (IB Section 6) and informed consent form for subject
Other malignant neoplasms (e.g., pancreatic cancer and malignancy when used with insulin) [potential risk]	Theoretical concern pancreatic cancer associated with GLP-1 based therapies (DPPIV-inhibitors and GLP-1R agonists) under evaluation by regulatory authorities (Egan; 2014), and has thus far concluded that a causal relationship cannot be established currently but they will continue to investigate as more data becomes available. Theoretical concern raised by EU regulatory authorities based on the biological plausibility of a tumour-promoting effect when a GLP-1R agonist is combined with insulin	No mitigation strategy

Identified/Potential/Other Risk of Clinical Significance	Data / Rationale for Risk	Mitigation Strategy
Hepatotoxicity [Potential risk]	One subject in the Phase III clinical programme developed probable drug induced liver injury with an asymptomatic elevation in ALT and total bilirubin although the cases had some atypical features and complicating factors. (Refer to Section 5.4.5.7 of the IB).	Specific eligibility and withdrawal criteria (See Section 4).
Patient population with severe renal Impairment (eGFR < 30 mL/min/1.73 m^2)o [Other risk]	Experience of albiglutide in T2DM patients with severe renal impairment is very limited Patients with severe renal impairment receiving albiglutide experienced a higher frequency of diarrhoea, nausea, and vomiting compared to patients with mild/moderate renal impairment (Refer to Section 5.4.6 and Section 6 of the IB).	Specific eligibility criterion (See Section 4). Risk communication via Guidance For Investigators (IB Section 6) and informed consent form for subject
Drug Interactions	Albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications (refer to Section 5.2.1.2, Section 5.2.5, and Section 6 of the IB). Drug interactions studies have been conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant PK or PD effects	Risk communication via Guidance For Investigators (IB Section 6) and informed consent form for subject
Pregnancy and Lactation	Studies in animals have shown reproductive toxicity. The potential risk to humans is unknown (Refer to Section 4.4.6 and Section 6 of the IB). 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.	Specific eligibility and withdrawal criteria (See Section 4) Risk communication via Guidance For Investigators (IB Section 6) and informed consent form for subject.

Identified/Potential/Other Risk of Clinical Significance	Data / Rationale for Risk	Mitigation Strategy
Study Design or Procedures		
Placebo-control	In subjects treated with placebo, hyperglycaemia may not improve or may worsen.	During the treatment period, the study will require individualisation of the insulin dose (both basal and meal-time insulin) in both treatment arms. (See Section 5.1.2.) aiming for euglycaemia
Albiglutide-placebo injection	In T2DM studies, albiglutide placebo injections were associated with a clinically relevant rate of injection site reactions (Refer to Section 5.4.5.6 of the IB)	Risk communication via Guidance For Investigators (IB Section 6) and informed consent form for subject. . Patients will be advised that when injecting in the same region, to use a different injection site each week
Other		
Basal and meal-time Insulin	Hypoglycaemia is the most common adverse effect associated with the use of insulins. The risk of hypoglycaemia increases with tighter glycaemic control (Refer to product labels).	Close monitoring for hypoglycemia and need for intervention via frequent contact with subjects who will self-monitor plasma glucose (See Section 5.1.2). During the treatment period, the study will require individualisation of the insulin dose in both treatment arms with a treat-to-target approach and a titration regimen based on FPG. (See Section 5.1.2.)
Diabetic ketoacidosis (DKA)	DKA is a risk in patients with T1DM, especially NOT1DM, where subjects may be unfamiliar with insulin therapy, clinical presentation or risk of DKA and/or have an intercurrent illness. Reduction of insulin dose to facilitate albiglutide treatment may theoretically increase the risk of DKA.	Subjects will be regularly monitored for DKA during the study, educated on DKA and plasma glucose levels maintained within acceptable clinical ranges using insulin titration schemes outlined in Section 5.1.2. Subjects advised to contact the site at any time with any concerns.

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; CHMP = Committee for Medicinal Products for Human Use; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; EMA = European Medicines Agency; FDA = Food and Drug Administration; FPG = fasting plasma glucose; GI = gastrointestinal; GLP-1R = glucagon-like peptide 1 receptor; GSK = GlaxoSmithKline; IB = Investigator's Brochure; ICF = informed consent form; LFT = liver function test; MTC = medullary thyroid carcinoma; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious AE; SC = subcutaneous; SU = sulfonylurea; ULN = upper limit of normal.

1.3.2. Benefit Assessment

In subjects with T2DM, the clinical data showed that once weekly albiglutide treatment (both the 30 mg and 50 mg doses), in an easy-to-use pen device, resulted in clinically relevant lowering of HbA1c when given as monotherapy and in combination with

metformin, sulphonylureas, thiazolidinediones (TZD) and basal insulin (reference: IB Section 5.5). Furthermore, the durability of the effect on these glycaemic parameters was shown over a study period of 3 years. In the two Phase III studies that compared albiglutide to insulin treatment (i.e., insulin glargine in one study and insulin lispro in the other), albiglutide therapy was associated with approximately 1.5-to 2-fold less symptomatic hypoglycaemia and with weight loss rather than weight gain (treatment difference of 1.5-2.6 kg).

In this current study in NOT1DM, where albiglutide treatment will be added to a regimen of basal/meal-time insulin therapy, the subject is expected to achieve similar glycaemic control to the group taking insulin alone, but with a reduced total daily insulin dose, reduced glycaemic variability (hypoglycaemia and hyperglycaemia) and reduced weight gain.

The anticipated benefit of albiglutide in NOT1DM is to delay or prevent deterioration of pancreatic β-cell function. Residual β-cell function is important for patients because the clinical course of their diabetes tends to be more stable, easier to manage, with less hyperglycaemia (including less DKA), less hypoglycaemia (including fewer serious episodes), a lower exogenous insulin requirement [Ostman, 2000; Madsbad, 1979; Home, 2003] and ultimately in the very long-term, fewer vascular complications [Steffes, 2003; DCCT, 1998], the latter will not be evaluated in this year-long study.

Finally, as a result of participating in a clinical trial, each subject will receive more contact with the study site, have diet and exercise advice reinforced at each visit, and more enhanced supervision of their diabetes than would be performed as part of their usual standard of care.

1.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimise risk to subjects participating in this study, the potential risks identified in association with albiglutide are justified by the anticipated benefits that may be afforded to patients with NOT1DM.

2. OBJECTIVE(S)

2.1. Primary Objective

- Determine the effect of albiglutide therapy versus placebo on endogenous insulin secretion over 52 weeks when added to standard of care in subjects with new onset type 1 diabetes mellitus (NOT1DM).

2.2. Secondary Objectives

- To assess the effect of albiglutide versus placebo on plasma glucagon concentration during a mixed meal tolerance test (MMTT)
- Determine the percentage of subjects meeting the definition of a responder (defined as having HbA1c $\leq$ 7.0% and mean daily insulin use < 0.5units/kg/day) and the

percentage of subjects achieving partial remission status (i.e., defined as subjects with Insulin Dose Adjusted A1c (IDAA1C) ≤ 9.0)

- To assess glycaemic control in both treatment groups as measured by HbA1c
- Determine differences in total daily insulin dose between treatment groups
- Determine any differences in significant hypoglycaemia (i.e., events with plasma glucose < 3.9 mmol/L and/or requiring third party intervention) between treatment groups
- Compare glycaemic variability between treatment groups, as measured by 72-hour continuous glucose monitoring (CGM) and 7 point glucose profile
- Determine the effect of albiglutide on body weight
- Assess the safety and tolerability of albiglutide in subjects with NOT1DM
- To evaluate the albiglutide PK profile in subjects with NOT1DM

2.3. Exploratory Objectives

- Assess the effect of albiglutide on T1DM-associated auto-antibodies (antibody to glutamic acid decarboxylase (anti-GAD) antibody to protein tyrosine phosphatase-like protein (anti-IA-2) and insulin autoantibody (IAA))
- Explore whether urinary C-peptide could be used in future phase III studies as an alternative to plasma C-peptide AUC from mixed meal testing as a measure of endogenous insulin secretion
- To evaluate the PK and PD (PK/PD) relationship between plasma albiglutide concentration and measures of glycaemic control (e.g., C-peptide, insulin use, HbA1c, etc) as data permit.
- To explore the PK/PD relationship between albiglutide and other potential efficacy, tolerability (e.g., nausea and vomiting), and safety endpoints as data permit
- Assess the effect of albiglutide on biomarkers associated with autoimmune pathology over 52 weeks in subjects with NOT1DM.
- Assess the effect of albiglutide on diabetes-related quality of life as measured by the Audit of Diabetes Dependent Quality of Life questionnaire (ADDQoL).
- Assess the effect of albiglutide on β-cell function in the context of the prevailing glucose response to the MMTT

3. INVESTIGATIONAL PLAN

3.1. Study Design

This Phase II, randomised, double-blind, parallel group, placebo controlled, multicentre study of 52 weeks treatment duration will evaluate the efficacy, safety and tolerability of weekly albiglutide versus placebo when added to insulin therapy in subjects with

NOT1DM and residual insulin production. The primary endpoint is mean change from baseline in mixed meal stimulated 2 hour plasma C-peptide AUC at Week 52.

Subjects within 8 weeks of diagnosis, who are receiving insulin treatment or have received insulin at some time between the date of diagnosis and the first dose of study drug, with one or more positive T1DM associated auto-antibodies, and a stimulated peak C-peptide > 0.2 nmol/L, signifying clinically relevant residual C-peptide production (as a measure of β cell function), will be eligible to enter the study.

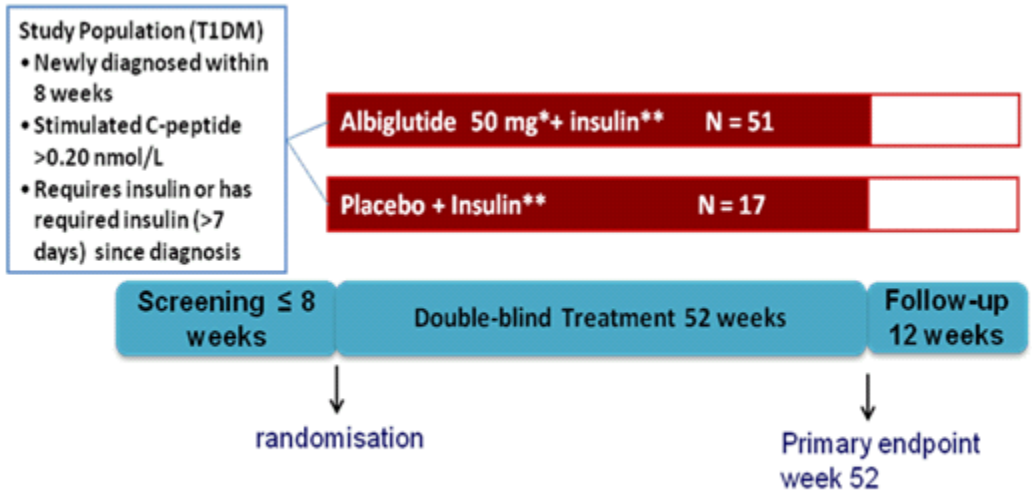
After screening, approximately 68 eligible subjects will be randomised in a 3:1 ratio such that:

- 51 subjects receive albiglutide 30 mg once weekly (with increase to 50 mg once weekly at Week 6 if the 30-mg weekly dose is tolerated) added-on to insulin therapy
- 17 subjects receive placebo once weekly added-on to insulin therapy

During the study, subjects will perform self monitoring of plasma glucose at least 4 times daily and adjust their basal and meal-time insulin requirements according to protocol-defined algorithm/guidance (See Section 5.1.2).

The total duration of a subject's participation will be approximately 72 weeks (up to 8 weeks of Screening, 52 weeks of treatment and 12 weeks of Post-treatment Follow-up) (Figure 1). Subjects will have 12 study centre visits and at least 14 telephone calls.

Figure 1 Study Schematic for GLP110933



*Albiglutide: start at 30 mg once weekly, increase to 50 mg once weekly at week 6 if 30 mg is tolerated
**Insulin dose adjusted according to protocol-defined algorithms

Potential events of pancreatitis will be adjudicated by an independent pancreatitis adjudication committee (PAC).

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

There will be no compassionate use of study medication once a subject completes or withdraws early from the study.

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 3), are essential and required for study conduct.

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

3.2. Discussion of Design

The design of this study and chosen endpoints i.e., randomised, double-blind, placebo-controlled with primary endpoint assessment after one year in T1DM subjects with documented residual β-cell function, are in line with guidance provided by both the EMA and FDA for the development of drugs aimed at preservation of β cell function in T1DM [FDA, 2008; EMA, 2012]. Currently there are no approved treatments for preservation of β-cell function in T1DM subjects.

Endogenous insulin secretion, as a key measure of β-cell function, is being assessed in this study by using the plasma C-peptide AUC following a mixed meal. When pancreatic β cells produce insulin, they also produce C-peptide in equimolar amounts. C-peptide has a longer half life than insulin and unlike insulin, experiences little first pass clearance by the liver. C-peptide connects the two components of pro-insulin and is released when the pro-hormone is activated [Gianani, 2005; Palmer, 2004]. Measurement of C-peptide under standardised conditions in response to a mixed meal challenge provides a sensitive, well accepted, and clinically validated assessment of endogenous insulin secretion and β cell function [Palmer, 2004].

As indicated in the EU guidelines for developing drugs that preserve β-cell function, pharmacological intervention will likely need to be initiated as soon as possible after manifestation of the disease to have a chance of showing a meaningful benefit (since greater than 80% of β-cell function may have been lost by the time of diagnosis and it continues to decline after diagnosis). Accordingly, in this study, subjects are to commence treatment with study drug within 8 weeks of diagnosis. This time interval was selected as a balance between maximising the potential to preserve the remaining β-cell function (by treating as early as possible after diagnosis) and feasibility (allowing time for subjects to consent to the study and to perform the screening assessments).

A stimulated C-peptide >0.2 nmol/L was selected as the cut-off for study entry as this level of C-peptide is the most widely used by researchers to represent clinically meaningful RBCF based on data from the DCCT [Diabetes Control and Complications Trial Research Group], 1998. The clinical importance of this cut-off was initially determined during the feasibility phase of the DCCT, in which metabolic parameters including fasting and post-prandial glucose levels, HbA1c, and daily insulin dosage, were compared among patients with stimulated C-peptide levels in 4 categories: >0.2 nmol/L; >0.1 - 0.2 nmol/L; >0.05 - 0.1 nmol/L; and ≤0.05 nmol/L [DCCT, 1987]. The group with a C-peptide >0.2 nmol/L had statistically significantly lower values for all of these parameters (indicating better metabolic control) than the other 3 groups. In the larger DCCT study, patients with stimulated C-peptide >0.2 nmol/L at study entry had a reduced risk of retinopathy (or progression of retinopathy), microalbuminuria, and hypoglycaemia (including severe hypoglycaemia), and a lower HbA1c than patients with C-peptide <0.2 nmol/L [DCCT, 1998; DCCT, 1997].

The control arm of this study will be placebo. To allow for a 3:1 randomisation ratio (albiglutide: placebo), historical data from the DEFEND-1 study [GlaxoSmithKline Document Number, 2011N125757_00] has been used as prior knowledge. In DEFEND-1, 53 subjects with similar inclusion/exclusion criteria were randomised to the placebo

group. Stimulated C-peptide data from a MMTT were collected at the same 52-week primary endpoint and therefore provide important safety and efficacy information for the placebo subjects. With this historical knowledge of placebo subjects, a Bayesian analysis method can be used which means fewer placebo subjects are required for this current study.

Subjects in both arms of the study will be on background insulin therapy (or will have required insulin for more than 7 days since diagnosis) - the standard of care for T1DM. Insulin may be titrated up or down to maintain glycaemic control throughout the study according to treat-to-glycaemic target protocol-defined insulin titration algorithms. Observing the drug effect versus placebo on top of standard of care background therapy will allow a better understanding of the efficacy, safety and tolerability profile of albiglutide in NOT1DM.

Data from 8 Phase III studies in subjects with T2DM (GLP108486, GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP114179 and GLP114130) have confirmed that both albiglutide 30 mg and 50 mg demonstrated robust efficacy and were generally well-tolerated in this patient population. Although a 30 mg dose of albiglutide was effective at controlling glycaemia for at least 2 years in many T2DM subjects, an increase in dose to 50-mg weekly offered additional benefit without significant safety issues (See IB for further details). The albiglutide dose in this study will start at 30-mg weekly and be increased to 50-mg weekly at Week 6 if the patient is able to tolerate the 30 mg weekly dose. Week 6 was chosen as the point for up-titration as it provides a sufficient length of time for subjects with NOT1DM to have their insulin doses stabilise and achieve steady-state exposures with 30 mg albiglutide (achieved following 4 to 5 weeks of once-weekly administration).

Forced up-titration will allow a more homogenous evaluation of albiglutide at its highest approved dose (for the treatment of T2DM) without the confounding effects of dose and time. Hyperglucagonaemia can also occur in NOT1DM. Increasing the dose of albiglutide to 50 mg at Week 6 offers the opportunity to further reduce hyperglucagonaemia, hence minimising β-cell stress. The higher dose will therefore maximise the potential benefit of albiglutide treatment on endogenous insulin secretion in subjects with NOT1DM.

Subjects experiencing GI intolerability on the 50 mg dose may decrease back to the 30 mg dose following discussion between the investigator and the medical monitor. This is included in the study design as it is important to keep subjects on albiglutide as long as possible to maximise the chance of being able to ascertain any therapeutic effect on β cell function.

Glucose variability will be assessed by 2 methods - the 7 point glucose profile and continuous glucose monitoring (CGM). Whilst the 7 point glucose profile is the established method for assessing glucose variability in clinical practice and in studies, CGM is gaining popularity and is recommended for use in diabetes trials by the EMA as it provides more detailed information on variability (glucose is sampled every 5 mins for 72 hours compared to the 7 point profile which only assesses glucose at 7 fixed time-points over a 24 hour period). However, it is not yet fully validated, it can be subject to

technical failures, measures glucose in tissue fluid rather than plasma, must be calibrated with fingerstick blood glucose values several times a day and is more valuable in looking for trends than absolute values. Hence both measures are included in the protocol.

Subjects will return for a follow-up visit at Week 64 (12 weeks after the end of the 52-week treatment period). The purpose of this follow-up is to determine if the effect of albiglutide treatment on endogenous insulin secretion is still apparent 12 weeks after stopping treatment (thus suggesting that albiglutide is disease modifying). Subjects will continue to follow the insulin titration algorithm described in Section 5.1.2 until completion of the Week 64 follow-up visit, to ensure equivalent glycaemic control is maintained in the 2 treatment arms throughout the follow-up period.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Approximately 68 subjects will be randomised to achieve 60 evaluable subjects. Note: if the withdrawal rate from the study is larger than expected, consideration will be given to replacing subjects who withdraw from the study.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s), product label, add other pertinent documents.

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.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Male or female, aged 18 to 30 years, inclusive, with a diagnosis of T1DM with an interval of 28-56 days between the initial diagnosis and the first dose of study drug. Documentation of the diagnosis of T1DM (and not just insulin deficiency), including the date of diagnosis, must be obtained from the diagnosing physician.
2. Currently requires insulin for T1DM treatment, or has required insulin therapy for T1DM (for ≥ 7 days) between the date of diagnosis and the first dose of study drug

   Note: subjects currently taking twice daily commercially available pre-mixed insulin will not be eligible.
3. Positive for at least one of the following autoantibodies typically associated with T1DM: antibody to glutamic acid decarboxylase (anti-GAD) antibody to protein tyrosine phosphatase-like protein (anti-IA-2) or an insulin autoantibody (IAA).

Please note: A subject who is positive for IAA and negative for the other autoantibodies will not be eligible if the subject has been using insulin for a total of ≥7 days.

4. Evidence of residual functioning pancreatic β-cells as measured by a peak stimulated C-peptide level > 0.20 nmol/L during the Screening MMTT when plasma glucose level is > 3.9 mmol/L (70 mg/dL) and ≤ 11.1 mmol/L (200 mg/dL).

   Note: the Screening MMTT should not be performed within one week of resolution of a DKA event.

5. Body mass index ≤ 32.0 kg/m^2.

6. Female subjects of childbearing potential (i.e., not surgically sterile and/or not postmenopausal) must be practicing adequate contraception (i.e., meeting one of the criteria defined below) from at least 14 days prior to the first dose of randomised study medication until the 12-week post-treatment Follow-up visit

   - Abstinence from penile-vaginal intercourse, when this is the female's preferred and usual lifestyle
   - Oral Contraceptive, either combined or progestogen alone
   - Injectable progestogen
   - Implants of etonogestrel or levonorgestrel
   - Estrogenic vaginal ring
   - Percutaneous contraceptive patches
   - Intrauterine device or intrauterine system that has a failure rate of less than 1% per year when used consistently and correctly as stated in the product label
   - 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 the site personnel's review of subject's medical records; medical examination of the subject and/or semen analysis; or interview with the subject on his medical history.
   - Male condom **combined with a female** diaphragm, either with or without a vaginal spermicide. [**UK only**: this method of contraception is acceptable only if used with a vaginal spermicide].

7. Able and willing to provide written informed consent and to comply with all study procedures.

4.3. 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.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Severe gastroparesis i.e., requiring therapy within 6 months prior to Screening
2. History of acute or chronic 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).
3. History of significant gastrointestinal surgery that in the opinion of the investigator is likely to significantly affect upper gastrointestinal or pancreatic function (e.g. gastric bypass and banding, antrectomy, Roux-en-Y bypass, gastric vagotomy, small bowel resection, or surgeries thought to significantly affect upper gastrointestinal function)
4. Personal history or family history of thyroid medullary carcinoma or multiple endocrine neoplasia type 2 (MEN2)
5. History of cancer that has not been in full remission for at least 3 years before Screening. (A history of squamous cell or basal cell carcinoma of the skin, or treated cervical intraepithelial neoplasia I or cervical intraepithelial neoplasia II is allowed)
6. Fasting triglyceride level >750 mg/dL at Screening. Subjects may be re-tested once during screening, and if the value no longer meets the exclusion criterion, the subject can be randomly assigned to treatment
7. Estimated Glomerular Filtration Rate (eGFR) ≤30 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease (MDRD) formula
8. Haemoglobinopathy that may affect proper interpretation of HbA_{1c}
9. Alanine aminotransferase (ALT) >2.5 × upper limit of normal (ULN) and bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
10. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). [Chronic stable hepatitis B and C are acceptable if subject otherwise meets entry criteria and are not on active antiviral treatment (e.g., presence of hepatitis B surface antigen or positive hepatitis C test result within 3 months of screening)]
11. Any clinically significant co-morbidity or abnormality (including psychiatric disorder, any other autoimmune endocrinopathy e.g., primary autoimmune hypothyroidism, hypoadrenalism, coeliac disease etc) that in the opinion of the Investigator, may pose additional risk in administering study medication or trial participation
12. Female subject is pregnant (confirmed by laboratory testing) or lactating
13. Known allergy to any GLP-1 analogue, insulin, or excipients of albiglutide
14. Treatment with any oral anti-diabetic medication within the prior 30 days or 5 half-lives of that medication, whichever is longer.
15. Use of immunosuppressants, intravenous immunoglobulin, oral or systemically injected glucocorticoids within the 3 months before randomisation or high likelihood of a requirement for prolonged treatment (>1 week) in the year following randomisation. However, short courses of oral steroids (single dose or multiple doses

for up to 7 days) may be permitted provided these cases are discussed with the medical monitor. Inhaled, intra-articular, and small quantities of non-potent topical corticosteroids are allowed

16. Receipt of any investigational drug within the 30 days or 5 half-lives, whichever is longer, before Screening, a history of receipt of an investigational anti-diabetic drug within the 3 months before randomisation, or receipt of albiglutide in previous studies

4.4. Withdrawal Criteria

Any subject who discontinues randomised study medication for any reason, after receiving at least one dose, will be asked to remain in the study and attend selected visits (see below) for collection of long-term efficacy and safety data (i.e., withdrawal of study drug does not require withdrawal from the study).

Every effort should be made to keep subjects in the study. The reasons for subjects discontinuing study medication and/or not completing the study will be recorded.

Consideration will be given to replacing subjects who withdraw from the study.

Reasons for study drug discontinuation

- These AEs **will** require study drug withdrawal:
  - Elevation of liver function test results according to the criteria in Section 6.4.9,
  - Severe allergic/hypersensitivity reactions that are considered by the investigator to be attributable to randomised study medication or without a likely alternative etiology (see Section 6.4.14)
  - Confirmed acute or chronic pancreatitis (see Section 6.4.15)
  - Confirmed medullary thyroid cancer
- AE, which, in the opinion of the investigator or subject precludes continuation of dosing
- Loss to follow-up (the investigator must make every effort to contact subjects lost to follow-up)
- Study closed/terminated or Investigator site closed
- Pregnancy or intention of becoming pregnant
- Protocol deviation (the investigator should discuss the protocol deviation with the sponsor before withdrawing study drug)
- Subject decision (reason to be documented in the electronic case report form (eCRF), if specified by the subject)
- Investigator discretion

Subjects who discontinue study medication will be asked to continue to attend the study visits where a MMTT is performed through to Week 64 (i.e., Week 16, Week 28, Week 52 and Week 64). During these visits where a MMTT will be performed, HbA1c, weight, AEs, hypoglycaemia and insulin usage will also be assessed. Subjects will also be asked to continue completing diaries for insulin usage and hypoglycaemia events. Additionally, the insulin titration algorithm/guidelines should continue to be followed through to Week 64.

While participating in the study, subjects should not receive any additional antidiabetic medication (except insulin) or investigational agents until after the Week 64 visit.

Reasons for withdrawal from the study

- AE which precludes continued follow-up in the study. Note: All AEs and SAEs will be followed until resolution, until the condition stabilises, or until the subject is lost to follow-up as described in the SPM.
- Lost to follow-up (the investigator must make every effort to contact subjects lost to follow-up).
- Study closed/terminated or Investigator site closed
- Protocol deviation (the investigator should discuss the protocol deviation with the sponsor before withdrawing a subject).
- Subject decision (reason to be documented in the eCRF, if specified by the subject)
- Investigator decision (e.g., in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being).

Note: Use of a prohibited medication constitutes a protocol deviation. Continuation of the subject in the study will be discussed with the medical monitor and the decision of continuation or withdrawal will be documented.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Subjects will be considered withdrawn from the study if they stop participating in the study and no longer attend visits. Each subject who withdraws should have an early withdrawal visit as soon as possible after deciding to withdraw. The assessments to be

performed at the early withdrawal visit are specified in the Time and Events Table (Table 3).

The half-life of albiglutide is approximately 5 days, and significant therapeutic concentrations can persist for up to 5 half-lives (3 to 4 weeks) after discontinuation. Therefore, the investigator should use caution when prescribing treatment after the withdrawal of active study medication taking into consideration the long half-life of albiglutide (see Section 5.6.2 for prohibited anti-diabetic medications for subjects discontinuing study medication early but still participating in the study), taking into consideration the long half-life of albiglutide.

4.5. Screening/Run-in 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, and respond to queries from Regulatory authorities, a minimal set of screen failure information will be collected including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

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 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 (sc) injection in the abdomen, thigh or upper arm region. The 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. The pens will deliver either 30 mg of albiglutide, 50 mg of albiglutide, or albiglutide 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 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 SPM.

Concomitant Insulin treatment

Concomitant insulin treatment (basal and meal-time insulin) should be used according to Section 5.1.2 but will not be provided by GSK. Subjects should be instructed on the use and storage requirements for insulin and will administer insulin as prescribed by their physician and in accordance with the package insert.

5.1.1. Investigational Product Administration During the Treatment Period

Investigational product (albiglutide or albiglutide matching placebo) will be administered once weekly by sc injection in the abdomen, thigh or upper arm region, from Baseline through to Week 52. The starting dose of albiglutide will be 30 mg once weekly and will be increased at Week 6 to 50 mg once weekly if the 30-mg weekly dose is tolerated. Subjects randomly assigned to albiglutide matching placebo will also go through the increased dose procedure to maintain study blind.

Note: if a subject experiences tolerability issues due to gastrointestinal AEs (e.g., nausea, vomiting or diarrhoea), the investigator should discuss the case with the medical monitor and a decision to decrease the dose back to 30 mg once weekly may be made. Decreasing the dose because of hypoglycaemia should not occur, the insulin dose should be adjusted instead.

Albiglutide (or albiglutide matching placebo) may be administered at any time of day without regard to meals. It should be administered once a week on the same day each week. The day of weekly administration can be changed if necessary provided the last dose was administered ≥ 4 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 has been > 3 days since the missed dose, subjects should wait and administer their next regularly scheduled weekly dose.

If a subject misses ≥ 2 consecutive doses, the investigator should contact the medical monitor (with details on why the doses were missed). The medical monitor will decide (on a case by case basis) whether the subject should be withdrawn from the study for a protocol deviation.

5.1.2. Insulin Titration

Subjects will take insulin as prescribed by the investigator throughout the study from Screening through to the follow-up visit. Note: subjects currently taking twice daily commercially available pre-mixed basal and meal-time insulin will not be eligible for the study.

It is important to ensure that subjects in both groups receive appropriate glycaemic control up to and including the follow-up visit (Week 64). All subjects should self monitor their plasma glucose values as detailed in Section 6.3.2.2. The investigator will provide guidance and education on the insulin regimen according to local clinical practice and will recommend dose adjustments at the regular study visits/telephone calls following the algorithm and guidance provided in Section 5.1.2.1 and Section 5.1.2.2 and based on the subject's self monitored plasma glucose values.

However, it is important that the Investigator base the decision to adjust the insulin dose on all available information, hypoglycaemia and/or hyperglycaemia (regardless of symptoms), urine ketone testing, previous responses to dose adjustments and plasma glucose measurements. Basal and meal-time insulin should be titrated up or down according to the algorithm/guidance in Table 1 and Table 2 to maintain equivalent glycaemic control in both treatment groups throughout the study. The investigator should communicate with the medical monitor if there is any doubt on insulin dose adjustment.

NOTE: the use of a GLP-1R agonist, (albiglutide) is expected to decrease the need for exogenous insulin. Therefore, the investigator will need to ensure careful follow-up of each subject accordingly, particularly during the first few weeks of treatment and reduce insulin doses if the subject experiences hypoglycaemia or there is a significant risk of hypoglycaemia.

Telephone calls (if there is no scheduled study visit) must take place at least weekly between the investigator and subject from Baseline to Week 16, as well as at Week 22, Week 34 and Week 46, and as required until the end of the follow-up phase, in order to optimise insulin titration. It is recommended that the investigator calls the subjects every 3-5 days during the first 2 weeks of randomised therapy and for 2 weeks after Week 6 when the study drug dose is increased. The investigator should consider increasing the frequency of telephone calls to optimise insulin titration if the subject's glycaemic control is erratic, or if there are associated clinical conditions that may impact on glycaemic control.

Subjects should be advised that they may contact the site at any time they would like advice or guidance on insulin dose adjustments or any concern about possible glycaemic and metabolic complications such as hypoglycaemia or ketoacidosis in particular.

Additionally, subjects should check their urine frequently, as directed by the study investigator, with Ketostix against the colour chart provided in line with usual clinical practice and seek medical attention as appropriate. The following guidance is provided:

- If the Ketostix identifies a small amount of urinary ketones and the subject is otherwise well, this may be associated with a period of fasting, or the subject may need to increase their insulin dose slightly
- If the Ketostix identifies a moderate or large amount of ketones, particularly if the plasma glucose is elevated, or the subject is unwell with an intercurrent illness, this may indicate DKA. The subject should seek urgent medical advice, either by telephone or in person from the physician who normally manages their T1DM or acute medical services if their regular physician is unavailable

Note: nausea and vomiting may be side-effects associated with albiglutide treatment but may also be symptoms of DKA. Subjects should be advised to check their urine more frequently during episodes of nausea and vomiting and to seek medical attention as appropriate.

5.1.2.1. Basal Insulin Titration

Both treatment arms will follow the same basal insulin titration algorithm during the treatment period.

In the absence of fasting plasma glucose (FPG) <4.1 mmol/L in the previous week, or a nocturnal hypoglycaemia event, adjustment of basal doses should be as described in Table 1. It should be based on the mean (or single value if only 1 is available) of the subject's self-monitored plasma glucose values measured before breakfast on ≥ 2 consecutive days in the week before the study visit/telephone contact, as shown in Table 1. At the investigator's discretion, basal insulin dose may be temporarily discontinued.

Table 1 Titration Algorithm for Basal Insulin

Before Breakfast Plasma Glucose[1]		Adjustment of Basal Insulin (U)
mmol/L	mg/dL	
<3.1[2]	<56[2]	-4
3-1 – 4.0[3]	56 - 72[3]	-2
>4.0 – 5.5	>72 – 99	No adjustment
>5.5 –7.8	>99 – 140	+2
>7.8	>140	+4

1. Mean of 2 or more consecutive days' measurements in the previous 7 days.
2. Investigator may defer adjustment if there is an obvious reason for the low value such as a missed meal or may interrupt or temporarily discontinue insulin, if appropriate.

5.1.2.2. Meal-time Insulin Titration

Meal-time insulin dose adjustment cannot be fully corrected, unless basal insulin doses have been optimised as far as possible. Both treatment arms will follow the same meal-time insulin titration guidance during the treatment period (Table 2). However, this is provided as guidance only as the meal-time insulin dose will be contingent upon, in particular, the planned carbohydrate caloric consumption, physical activity level, and the results of home plasma glucose monitoring.

The dose adjustment of meal-time insulin is based on the plasma glucose values ≥ 4 hours after the previous meal. It is recommended that dose adjustments of meal-time insulin be made on the mean (or single value if only one available) of values from ≥ 2 consecutive days in the week just prior to the visit/phone contact as outlined in Table 2. At the investigator's discretion, bolus insulin at one or more meal-times may be interrupted.

Table 2 Titration Guidance for Meal-time Insulin

Plasma glucose 4 or more hours after the preceding meal[1, 2]		Adjustment of meal-time insulin (U)[2]
mmol/L	mg/dL	
<3.9 without obvious explanation	<70 without obvious explanation	-1-2[3]
3.9 – 5.5	70 – 99	No adjustment
5.6 – 7.7	100 – 139	+1
7.8 – 9.9	140 – 179	+2
≥10.0	≥180	+3

1. If basal dose is not optimal following this algorithm may lead to overdosing
2. Mean of 2 or more consecutive days' measurements over previous 7 days
3. At the investigator's discretion, a meal-time insulin dose may be suspended

It is strongly recommended that the algorithms in Table 1 and Table 2 are followed at all visits and telephone contacts until the Week 64 Follow-up visit. Any deviation from the algorithm and the detail of reasons for this deviation must be recorded by the Investigator. Any deviation that does not have a valid reason will be recorded as a protocol deviation.

5.1.3. Surveillance of Insulin Titration

Surveillance of insulin titration will be performed centrally. Within approximately 24 hours after a subject's study visit/telephone contact, the Investigator must ensure that the following data are available for review by the medical monitor:

- Subject's self-monitored plasma glucose (SMPGs) on ≥ 2 consecutive days in the week prior to the visit/telephone contact
- Insulin doses on ≥ 2 consecutive days in the week prior to the visit/telephone contact
- Insulin doses recommended until the next visit/telephone contact
- Comments on any deviation to the titration algorithm/guidance

The data regarding titration deviations will be reviewed by the medical monitor. Based on this information, an inquiry as to why the Investigator chose to deviate from the titration algorithm may be made – in particular details of any SMPG readings, time, and date, or hypoglycaemic symptoms, used in such a decision are needed. Not all deviations will lead to inquiry. When the Investigator receives an inquiry, a response with the reasons for not adhering to the titration guideline should be received within approximately 3 days. Depending on the response additional inquiries may be sent.

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 to execute each randomisation and initiate shipment of the investigational product once a subject has met all prerequisites for randomisation and has completed all scheduled screening procedures.

Approximately 68 subjects will be randomly assigned to 1 of the following 2 treatment groups in a 3:1 ratio such that

- Approximately 51 subjects are assigned to albiglutide 30 mg weekly (with treatment-masked increase to 50 mg weekly at Week 6) + background insulin
- Approximately 17 subjects are assigned to albiglutide matching placebo + background insulin

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 SPM.

5.3. Blinding

This will be a double-blind study. Study treatment with albiglutide and matching albiglutide placebo is blinded to subjects, study personnel and sponsor.

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 required) 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.

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.

If a subject is unblinded, withdrawal of that subject from study treatment/study will be at the discretion of the investigator.

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 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

Investigational product accountability will be done for albiglutide/matching placebo at each study visit after the baseline visit through the end-of-treatment visit (at Week 52) inclusive. Subjects will be instructed to return all unused investigational product and used injector pens at each visit (with the exception of Week 2 where only used injector pens need to be returned) in order to perform drug accountability and determine compliance.

Acceptable overall compliance for this study will be ≥80% for albiglutide and albiglutide matching placebo.

If a subject misses 2 or more consecutive doses of randomised study medication, the investigator should contact the medical monitor, who will make a decision (on a case by case basis) on whether the subject should be withdrawn from study drug or the study for non-compliance.

Background insulin will be taken as prescribed by the investigator and in accordance with the respective package insert.

5.6. Concomitant Medications and Non-Drug Therapies

All concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

5.6.1. Permitted Medications and Non-Drug Therapies

Note: Albiglutide causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the development programme, drug interaction studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant pharmacokinetic or pharmacodynamic effects (see GlaxoSmithKline Document Number, RM/2006/00602/07). However, investigators should use clinical judgement and caution when prescribing concomitant medications.

The following are permitted:

- Insulin

  Insulin use will be recorded in diaries by subjects, as described in the Time and Event Table (Table 3) and Section 6.3.2.5. The insulin-use data will be reviewed by the investigator for accuracy and completeness. Subjects should use a basal/bolus insulin regimen. Insulin pumps and twice daily commercially available pre-mixed insulin are not permitted. Insulin dosage may be changed and insulin therapy may be interrupted or re-started whenever necessary to help the subject achieve and maintain optimum glycaemic control. See Section 6.2 for description of diabetic standard of care.

- As-needed use of other prescription and over-the-counter medications at the discretion of the investigator

Although stable doses of all concomitant medications are preferable, changes in medications during the study to appropriately treat clinical conditions that might arise are allowed.

Investigators must adhere to the local labeling of the respective country (e.g., the summary of product characteristics in relevant European countries) for all non-excluded medications.

5.6.2. Prohibited Medications and Non-Drug Therapies

Subjects must not use any of the following medications:

- Twice daily commercially available pre-mixed insulin.
- Insulin pumps.
- Anti-diabetic medications other than insulin and the treatment they have been randomly assigned to (Note: even if a subject discontinues randomised study medication, he/she should not receive any other GLP-1R agonist, oral anti-diabetic medication (e.g., metformin, sulphonylurea, thiazolidinediones, Dipeptidypeptidase-IV [DPP-4]) or an investigational agent until after the Week 64 visit)
- Immunosuppressants and intravenous immunoglobulin
- Prescription and over-the-counter weight loss drug
- Prolonged treatment (>1week) of oral or systemically injected glucocorticoids

If a subject receives a prohibited medication, a protocol deviation will be reported and continuation in the trial will be discussed with, and agreed upon, by the medical monitor.

5.7. Treatment after the End of the Study

After completion of the Week 52 visit, subjects will stop randomised study medication. Subjects will continue to receive insulin therapy (basal-bolus insulin) as prescribed by their health care provider but must continue to adhere to the protocol-defined insulin

titration algorithm/guidelines until Week 64. Subjects will return to the study centre at Week 64 for the follow-up visit and will have then completed the study.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient'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 T2DM, the highest dose of albiglutide administered was 100 mg sc 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).

Excess insulin administration may cause hypoglycaemia and hypokalaemia. If an overdose of insulin occurs, the investigator should consult the approved product label for advice. Subjects should be watched closely even after treatment of the acute event; recurrence should be managed appropriately

6. STUDY ASSESSMENTS AND PROCEDURES

This section includes a brief description of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Table 3) and the schedule of telephone calls is listed in Table 4. Detailed procedures for obtaining each assessment are provided in the SPM.

Table 3 Time and Events Table

Study Procedure	Visit	Screening		Treatment To include at least weekly telephone contact (where there is no study visit) from Baseline to Week 16 – see Table 4 [2]									Off treatment follow-up	Early Withdraw[27]
				Baseline										
	Visit	1	2[3]	3	4	5	6	7	8	9	10	11	12	
	Week[1]	-8 to 0		0	2	4	6	8	16	28	40	52	64	
Written informed consent		x												
Demography and history (medical, disease, therapy)		x												
Review eligibility criteria		x	x	x										
Provide diet, exercise and home glucose monitoring advice			x	x	x	x	x	x	x	x	x	x		
Efficacy assessments														
Mixed meal tolerance test[4]			x						x	x		x	x	
7 point glucose profile[5]				x						x		x		
72 hour continuous glucose monitoring [6]				x						x		x		
Review glucose monitoring/insulin dose with subject			x	x	x	x	x	x	x	x	x	x	x	
ADDQoL				x								x		
Safety assessments														
Concomitant medication		x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination[7]		x		x					x	x	x	x	x	x
Vital sign[8]		x		x	x	x	x	x	x	x	x	x	x	x
12-lead ECG[9]				x		x			x	x	x	x	x	
Adverse events		X[10]	X[10]	x	x	x	x	x	x	x	x	x	x	x
Assess for hypoglycaemic events[11]			x	x	x	x	x	x	x	x	x	x	x	x
Laboratory assessments														
HbA_{1c}				x		x		x	x	x	x	x	x	x
Triglycerides (fasting)[12]		x												
T1DM associated auto-antibody titres[13]		x[14]				x			x	x	x	x	x	
Immunogenicity [15]				x	x	x	x	x	x	x	x	x	x	
Haematology[16]/chemistry[17]		x		x	x	x		x	x	x	x	x	x[18]	x
Urinalysis[19]		x		x		x		x	x	x	x	x	x[18]	x
Pharmacogenetics[20]				x										
Pharmacokinetic sample[21]						x	x	x	x					
PBMC Biomarker sample [22]				x		x			x	x	x	x	x	

Study Procedure		**Screening**		**Treatment To include at least weekly telephone contact (where there is no study visit) from Baseline to Week 16 – see Table 4 [2]**									**Off treatment follow-up**	**Early Withdraw[27]**
				Baseline										
	Visit	**1**	**2[3]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
	Week[1]	**-8 to 0**		**0**	**2**	**4**	**6**	**8**	**16**	**28**	**40**	**52**	**64**	
Serum Biomarker sample [23]				x		x			x	x	x	x	x	
Pregnancy test[24]		U		U		U		U	U	U	U	U	U	U
HBsAg, and hepatitis C antibody[25]		x												
Dispense Investigational product (IP)				x		x	x	x	x	x	x			
IP compliance					x	x	x	x	x	x	x	x		x
Register visit into IVRS[26]		x	x	x	x	x	x	x	x	x	x	x	x	x

ADDQoL = audit of diabetes dependent quality of life; ECG = electrocardiogram; HbA_{1c} = glycosylated haemoglobin, HBsAg =-hepatitis B surface antigen ;IVRS = interactive voice response system, PGx = pharmacogenetics; S = serum; U = urine, PBMC = peripheral blood mononuclear cells; T1DM = type 1 diabetes mellitus

1. Study visits from Baseline through to Week 8 will have a visit window of ±3 days. Study visits from Week 16 through to Week 64 will have a visit window of ±7 days. Subjects will not be considered out of compliance if visit windows extend because of events (e.g., holidays, vacations, personal emergencies). However, determination of the maximum visit window deviation will be at the discretion of the medical monitor.
2. Telephone call to occur between study visits at least weekly from Baseline to Week 16 (it is recommended that calls occur every 3-5 days during the first 2 weeks of randomised treatment and after Week 6 when the study drug dose is increased), and at Week 22, Week 34, Week 46 and as required to advise subjects on insulin dose adjustments, adverse event (AE) monitoring, hypoglycaemia monittoring, and concomitant medication usage.
3. Visit to be performed once other screening tests indicate eligibility.
4. See Section 6.3.2.1 for details on the MMTT. Screening MMTT to be performed once other screening test indicate eligibility and at least 28 days from the date of diagnosis of T1DM. Take a urine sample at 120 mins post- MMTT for assessment of urinary C-peptide and urinary creatinine. Subjects to void their bladders just prior to the start of the MMTT.
5. 7 point glucose self-monitoring: before and 2 hours after breakfast, lunch and dinner, at bedtime, on one day in the week prior to each scheduled assessment (to coincide with one of the days that the CGM is conducted).
6. To be performed in the week prior to the visit. Subject to make an additional visit to the study site to have the CGM monitor fitted/inserted
7. Perform complete physical examination at Screening and Week 52. Perform brief physical examination at other time points.
8. Vital signs include weight, blood pressure, and heart rate (pulse). Height to be measured at Screening only. Calculate body mass index at Screening.
9. All 12-lead ECGs to be performed in triplicate (approx 10 mins apart) and before measurement of vital signs and collection of blood samples for laboratory testing. Subjects to be semi-recumbent for 10 to 15 minutes before ECGs.
10. Only diabetic ketoacidosis SAEs, hypoglycaemia SAEs and SAEs thought to be related to study procedures need to be reported during Screening
11. See Section 6.4.2 for hypoglycaemia event criteria and reporting requirements. . Urine ketostix to be performed regularly according to clinical practice (see Section 5.1.2)
12. Fasting is defined as no food or drink (except water) for at least 8 hours before blood draw.
13. Anti-GAD, anti-IA2, IAA
14. If results are required quickly for eligibility purposes, local labs may be used for the Screening sample only. If local labs are used, a screening sample must also be sent to the central lab.

15. Immunogenicity sampling is to be done prior to dosing throughout study
16. Haematology to include complete blood count with haemoglobin, other red blood cell indices, white blood cell count differential, and platelet count.
17. Clinical chemistry to include: glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, uric acid, magnesium, phosphorus.
18. If abnormal at Week 52
19. Urinalysis to include: specific gravity, pH, glucose, protein, blood by dipstick (if warranted, a microscopic evaluation will be completed).
20. Blood sample for pharmacogenetics (PGx) can be collected at any time during the study after the PGx informed consent has been obtained and the subject has been randomly assigned to a treatment group.
21. 2ml blood sample. Sample at Week 4 and Week 6 to be taken at least 2 days (48 hours) after the most recent dose of study medication and at any time prior to the next scheduled dose. At Week 6 or any subsequent visit where up or down titration of albiglutide/matching albiglutide placebo coincides with PK sampling, the PK sample must be taken prior to titration, such that it is taken no more than 16 hours prior to the subsequent dose. At Week 8 and Week 16, sample to be collected at least 2 days (48 hours) after a dose but not within 4 days of another sample.
22. 8ml blood sample to achieve approx 4 million viable PBMC sample – split into 2 samples
23. 5ml blood sample to achieve approximately 2 ml serum sample – split into 3 samples
24. Pregnancy test for women of child-bearing potential only and at any other time that pregnancy is suspected (U = urine).
25. If hepatitis C antibody positive, RNA polymerase chain reaction should be performed on the same sample to confirm the result.
26. Randomisation to occur at baseline visit.
27. If a subject discontinues study medication, they will be asked to continue to participate in the study and continue to attend study visits where a MMTT is performed. During these visits, as well as a MMTT, HbA1c, weight, AEs, hypoglycaemia and insulin usage should be assessed. Subjects should also continue to complete their diary and must adhere to the insulin titration algorithm/guidelines as defined in the protocol through to Week 64. If the subject refuses to continue attending these visits after stopping study medication, complete this early withdrawal visit.

Table 4 Time and Events Table – Telephone Calls

Study Procedure		Treatment (telephone calls to be performed as a minimum at the time points specified (± 3 days) and as required for appropriate management of the subject													
	Week	**1[1]**	**3**	**5**	**7**	**9**	**10**	**11**	**12**	**13**	**14**	**15[2]**	**22[2]**	**34[2]**	**46[2]**
Review glucose monitoring with subject[3]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Review the need for insulin dose titration[3]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent medication		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess for hypoglycaemic events[4]		x	x	x	x	x	x	x	x	x	x	x	x	x	x

1. Every 3-5 days during the first 2 weeks and for 2 weeks following study drug increase at Week 6
2. Telephone calls as necessary from Week 16 through to the end of the study to advise subjects on insulin dose adjustments, adverse event (AE) monitoring, hypoglycaemia and diabetic ketoacidosis monitoring
3. Review the glucose meter readings and adjust basal insulin and meal-time insulin doses as per Table 1 and Table 2, respectively
4. See Section 6.4.2 for hypoglycaemia event criteria and reporting requirements. Urine ketostix to be performed regularly according to clinical practice

6.1. Critical Baseline Assessments

Before any study-specific procedure is performed, valid informed consent must be obtained.

The Baseline visit will take place after information collected during Screening has been reviewed and all eligibility criteria have been confirmed.

Critical baseline assessments will include: MMTT (Screening test to be used for Baseline), 7 point glucose profile, 72-hour continuous glucose monitoring, insulin usage, HbA1c, and body weight.

Cardiovascular medical history/risk factors will be assessed at baseline.

6.2. Standard of Diabetic Care

Intensive monitoring and care will be provided according to current standards of care for patients with T1DM. Diabetes care will include consultations with a nutritionist or dietitian and/or a diabetes educator according to the local institution's guidelines for newly diagnosed T1DM. Study centres are expected to work with each subject to optimise glycaemic control, with a target HbA_{1c} level of 7.0 %. Diabetes management (insulin therapy, diet, weight maintenance, exercise programmes, etc.) will be directed towards helping each subject reach this target or come as close to it as possible.

Subjects will monitor their plasma glucose levels as described in Section 6.3.2.2. At each visit, study staff will review the use of the plasma glucose monitor and the recent plasma glucose data with the subject. Insulin use is discussed in Section 6.3.2.5.

6.3. Efficacy

6.3.1. Study Endpoints

6.3.1.1. Primary Endpoint

- Mean change from baseline in stimulated (from MMTT) 2 hour plasma C-peptide area under the curve (AUC) at Week 52

6.3.1.2. Secondary Endpoints

- Mean change from baseline in stimulated (from MMTT) 2 hour plasma C-peptide AUC at Week 16, 28 and Week 64
- Maximum stimulated plasma C-peptide: the highest value at any time point during the 2 hour MMTT after the subject has ingested the mixed meal at Baseline, Week 16, Week 28, Week 52 and Week 64
- Mean change from baseline in plasma glucagon AUC (from MMTT) at Week 16, 28, 52 and Week 64.

- Percent of responders (as defined as subjects with HbA1c < 7.0% and insulin dose < 0.5 units/kg/day) at Weeks 4, 8, 16, 28, 40, 52 and 64
- Percent of subjects achieving insulin dose-adjusted haemoglobin A1c (IDAA1C) ≤ 9.0 at Weeks 4, 8, 16, 28, 40, 52 and 64
- Change from Baseline in HbA1c at Week 52 and HbA1c over time (i.e., at Weeks 4, 8, 16, 28, 40, 52 and 64
- Change from baseline in mean daily insulin use over the 3 days preceding the visit at Weeks 4, 8, 16, 28, 40, 52 and 64. The mean daily insulin use value will be calculated in units/kg/day, as the mean of the values of the total amount of insulin used per day on each of the 3 consecutive days
- Number of events of hypoglycaemia with confirmed self plasma glucose monitoring < 3.9 mmol/L and/or requiring 3rd party intervention (i.e., severe, documented symptomatic and asymptomatic events see Section 6.4.2) occurring > Week 24 and ≤ Week 52.
- Number and magnitude of hypoglycaemic (<3.9 mmol/L) and hyperglycaemic excursions (> 10.0 mmol/L) from the 7 point glucose profile at Baseline, Week 28 and Week 52
- Time spent with a plasma glucose <3.9 mmol/L, between 3.9 and 10.0 mmol/L, and >10.0 mmol/L, respectively as performed by 72-hour CGM at Baseline, Week 28 and Week 52
- Change from Baseline in body weight (kg) at Week 52 and Weight over time (i.e., at Weeks 2, 4, 6, 8, 16, 28, 40, 52 and 64)
- Pharmacokinetic endpoints include the following:
  - Population estimates of PK parameters (e.g., apparent clearance [CL/F], apparent volume of distribution [V/F], first-order absorption rate constant [K_a]), associated intersubject variability and residual error
  - Covariates and covariate effects on subject PK
  - Population estimates of PD parameters (e.g., Emax, EC_{50}), associated inter-subject variability and residual error if permitted by the data

6.3.1.3. Exploratory Endpoints

- Change from baseline in anti-GAD, anti-IA-2 and IAA antibody titres at Week 4, Week 16, Week 28, week 40, Week 52 and Week 64
- Correlation of urinary C-peptide 120 minute after a mixed meal (urinary creatinine corrected) with MMTT C-peptide AUC assessed at Baseline, Week 16, Week 28, week 52 and Week 64
- Graphical or model-based exploration of PK/PD relationships between albiglutide exposure (e.g., steady state AUC) and selected PD endpoints if appropriate and permitted by the data

- Biomarker endpoint: PBMC and serum samples for exploratory biomarker analysis will be collected at various timepoints throughout the study (see Table 3). A decision on whether to analyse biomarker samples will be made after review of efficacy endpoints at the end of the study. Exploratory biomarkers may include CD8-positive antigen-specific T-cells and biomarkers for β-cell death
- Change from baseline in ADDQoL global and domain scores and overview item scores at week 52.
- β-cell function, expressed as an insulin secretion parameter, will be estimated by modelling glucose and c-peptide concentrations. The modelling process will include, but is not limited to, the deconvolution of c-peptide data in the context of the prevailing glucose response to the meal

6.3.2. Efficacy Assessments

6.3.2.1. Mixed Meal Tolerance Test

The MMTT will be performed according to the schedule in the Time and Events Table (Table 3). Further details on the procedure are provided in the SPM.

For the 3 days before the MMTT, subjects will be asked to eat a balanced diet consistent with advice provided by a nutritionist or dietitian and/or diabetes educator according to the local institution's guidelines for NOT1DM and not to make major changes from their customary exercise regimens.

On the evening before the MMTT, subjects should eat a full, usual meal, then fast from 21:00 h (9 PM) until the MMTT is completed. Water, black coffee, or black tea (with no sugar or artificial sweeteners) is allowed during the fast and test.

The MMTT will start in the morning and the time the test is started should be kept as consistent as possible. Prior to the test, plasma glucose will be measured using a finger-stick test and must be > 3.9 mmol/L (70 mg/dL) and ≤ 11.1 mmol/L (200 mg/dL) for the MMTT to be performed. If the glucose is outside this range, the MMTT must be rescheduled.

On the morning of the test, subjects will modify their insulin regimen as follows:

- Withhold the morning dose of long- or intermediate-acting insulin
- No short-acting insulin for at least 6 hours before the test
- No rapid-acting insulin for at least 2 hours before the test

Immediately prior to the test, subjects should void their bladder.

Subjects will consume a standardised amount of a nutritional drink (6 mL per kg body weight up to a maximum of 360 mL). The time when the subject starts drinking is defined as Time 0. The subject will drink the nutritional drink within 5 minutes or less.

Blood samples will be taken to assess levels of C-peptide, glucose and glucagon at

- 10 minutes before Time 0 (-10 minutes).
- Immediately before the subject starts drinking the nutritional drink (Time 0).
- 15, 30, 60, 90, and 120 minutes after Time 0.

A urine sample will be taken at 120 minutes after Time 0 to assess C-peptide and creatinine.

A snack appropriate for a subject with diabetes will be available immediately after the 120-minute blood draw. As soon as feasible after completing the MMTT, subjects will resume their usual insulin and diet regimens.

6.3.2.2. Self Monitoring of Plasma Glucose

All subjects should be instructed to measure and record plasma glucose values from their glucose meter at least 4 times a day at the suggested times for at least 2 consecutive days in the week before any study center/telephone contact

- Before breakfast
- Before lunch
- Before dinner
- At bedtime

All results of self plasma glucose monitoring will be stored in the subject's glucose meter and communicated to the study site as directed by the investigator. The investigator will review the glucose meter readings at the study visit/telephone call and adjust insulin doses as per Table 1 and Table 2. If a measurement is only available for 1 day, this will be used to assess the need for insulin dose adjustment but the site will need to explain to the subject the importance of having at least 2 daily measurements. Additional glucose meter monitoring should be performed as per local practice.

Weekly telephone calls (if there is no scheduled study visit) must take place between the investigator and subject from Baseline to Week 16, as well as at Week 22, Week 34, Week 46, and as required until the end of the follow-up phase, in order to optimise insulin titration. It is recommended that the investigator calls the subjects every 3-5 days during the first 2 weeks of randomised therapy and after Week 6 when the study drug dose is increased.

NOTE: the use of a GLP-1R agonist (albiglutide) is expected to decrease the need for insulin and, therefore, the investigator will need to ensure careful follow-up of each subject accordingly, particularly in the first two weeks after randomisation.

6.3.2.3. 7-Point Self-Monitored Plasma Glucose Profile

A 7 point glucose profile will be conducted at the times specified in the Time and Events Table (Table 3). Subjects should be instructed to measure and record plasma glucose values from their glucose meter at the following times:

- Before breakfast (at least 8 hours without food intake)
- 2 hours after breakfast
- Before lunch
- 2 hours after lunch
- Before dinner
- 2 hours after dinner
- At bedtime

6.3.2.4. 72-hour Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) will be conducted at the times specified in the Time and Events Table (Table 3). Three days before the visit, the subject should make an additional visit to the study site to have the continuous glucose monitor fitted/inserted. It should be worn for 3 consecutive days and be removed at the scheduled study visit. Whilst wearing the CGM, subjects should continue to monitor their plasma glucose as described in Section 6.3.2.2 and on one of the days, conduct the 7-point glucose profile as described in Section 6.3.2.3.

Subjects and their physicians will not have access to the CGM data during the period of monitoring.

6.3.2.5. Daily Insulin Use

Subjects will record their daily insulin use in a diary. This information will be collected for at least 3 days before Baseline, daily for the first 2 weeks and for at least 3 days preceding the telephone calls/visits at Week 3 through to Week 16, Week 22, Week 28, Week 34, Week 40, Week 46, Week 52 and Week 64. During each of these visits the investigator or designee will review the data recorded in the preceding 3 days and if errors or gaps are identified (e.g., if the subject did not take insulin and has not entered "0 units" the investigator will record the missing information from subject recall. Based on this information, mean daily insulin use over the 3 consecutive days (in units per kg body weight per day) will be calculated for each subject.

6.3.2.6. HbA1c

HbA1c will be recorded at visits as shown in the Time and Events Table (Table 3).

6.3.2.7. Body Weight

Body weight should be measured to the nearest 0.1 kg on a standard calibrated scale. Subjects should be dressed in light indoor clothes (no coat, jacket, etc) without shoes and with a voided bladder. (NB bladder should not be voided before completion of a MMTT). The same equipment should be used wherever possible.

6.3.2.8. Audit of Diabetes Dependent Quality of Life (ADDQoL)

The ADDQoL is a validated instrument for the assessment of the impact of diabetes on quality of life. The original instrument has undergone further development since its publication in 1999, and the current version, the ADDQoL 19 will be used in this trial ([Bradley, 1999; Bradley, 2002; Wee, 2006]. The ADDQoL is designed for use in clinical applications, and as an outcome measure in clinical trials evaluating new treatments, and was shown to be sensitive to a change in insulin regimen in the DAFNE trial [Amiel, 2002].

The ADDQoL consists of two overview items designed for audit purposes: generic "present QoL" and diabetes-specific "impact of diabetes on QoL". A further 18 items assess the impact of diabetes on a range of quality of life domains including physical functioning, symptoms, psychological well-being, social well-being, role activities and personal constructs. Respondents rate both impact of diabetes on applicable domains and also the importance of those domains for their QoL. Respondents also indicate if some domains are not relevant to them. The instrument thus yields a weighted global score calculated only on domains relevant to the respondent in addition to individual domain and overview item scores.

6.4. Safety

6.4.1. Safety Endpoints

- Hypoglycaemic Events
  - Incidence of hypoglycaemia (in total and by each category as defined by ADA criteria (see Section 6.4.2) overall and in 3 monthly intervals (i.e., from Baseline to Week 12, >Week 12 to ≤Week 24, >Week 24 to ≤Week 36, >Week 36 to ≤Week 52, >Week 52 to ≤Week 64
  - Incidence of hypoglycaemia with plasma glucose <3.1 mmol/L (< 56mg/dL) regardless of symptoms).
  - Incidence of daytime hypoglycaemia (in total and by category) (defined as hypoglycaemic episodes with an onset between 06:00 h and 00:00 h (inclusive) and nocturnal hypoglycaemia (in total and by category) defined as hypoglycaemic episodes with an onset between 00:01 h and 05:59 h (inclusive) will be determined.
  - Incidence of, and number of, hypoglycaemia with plasma glucose <3.9 mmol/l (< 70 mg/dL) regardless of symptoms) and/or requiring 3rd party assistance (i.e., severe, documented symptomatic and asymptomatic hypoglycaemic events) occurring > Week 24 and ≤ Week 52 (This is a secondary efficacy endpoint).
- Adverse events and serious adverse events
- Other adverse events of special interest (AESI) (for example, cardiovascular, gastrointestinal, pancreatitis, malignancies (including pancreatic cancer and thyroid cancer), injection site reaction, liver events, potential systemic allergic reactions,

atrial fibrillation/flutter, pneumonia, DKA [i.e., ketonuria/ketonaemia, hyperglycaemia and acidaemia])

- Assessment of clinical laboratory tests (haematology, biochemistry, urinalysis)
- Assessment of vital signs measurements, 12-lead ECGs and physical examinations
- Immunogenicity (e.g.,percentage of subjects developing anti-albiglutide antibodies and characterisation of anti-albiglutide antibodies)

The following sections provide further detail on the safety assessments. Planned timepoints for all safety assessments are listed in the Time and Events Table (Table 3). Unscheduled visits will occur as medically necessary.

Liver chemistry stopping and follow-up criteria and AEs are described in Section 6.4.9 and Section 6.4.10 respectively.

For some AESI, specific eCRF pages will be used to capture additional details about the events (e.g., cardiovascular including atrial fibrillation/flutter (Section 6.4.12), injection site reactions, pancreatitis, thyroid cancer, pneumonia).

6.4.2. Subject-Reported Hypoglycaemia Events

Subjects will be asked to report hypoglycaemic events that occur in a diary, which will be integrated with the clinical database at the end of the study. These hypoglycaemic events that are reported by subjects will be classified as defined by the ADA Workgroup on Hypoglycaemia [Seaquist, 2013].

Severe Hypoglycaemia

- Severe hypoglycaemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration

Documented Symptomatic Hypoglycaemia

- Documented symptomatic hypoglycaemia is an event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L)

Asymptomatic Hypoglycemia

- Asymptomatic hypoglycaemia is an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L)

Probable Symptomatic Hypoglycemia

- Probable symptomatic hypoglycaemia is an event during which symptoms typical of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤70mg/dL (≤3.9 mmol/L)

Pseudo Hypoglycemia

- Pseudo hypoglycaemia is an event during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L) but approaching that level

Any hypoglycemia event, regardless of intensity, that satisfies the definition of an SAE (Section 6.4.10.2) should be categorised as outlined in this section and reported appropriately on the SAE eCRF pages.

6.4.3. Physical Examination

Either a complete physical examination or brief physical examination will be performed at the time points specified in the Time and Events Table (Table 3).

The complete physical examination will include evaluation of the following organ or body systems:

- Skin (including injection site)
- Head, eyes, ears, nose, and throat
- Thyroid
- Respiratory system
- Cardiovascular system
- Abdomen (liver, spleen)
- Lymph nodes
- Central nervous system
- Extremities

The brief physical examination will include evaluation of the following organ or body systems:

- Skin (including injection site)
- Respiratory system
- Cardiovascular system
- Abdomen (liver, spleen)
- Central nervous system

6.4.4. Height and BMI

Height will be measured at screening only and Body Mass Index (BMI) will be calculated (using body weight at Screening) as:

BMI = weight (kg) / [height (m)]^2

Note: body weight is detailed under efficacy (Section 6.3.2.7)

6.4.5. Vital Signs

Assessment of vital signs (blood pressure and pulse rate) will be performed according to the schedule in the Time and events Table (Table 3). During visits where ECGs and blood samples are taken, the vital sign measurements will be taken after the ECG and before the blood draw.

Vital signs will be taken with the subject either in a semi-recumbent or seated position after at least a 5-minute rest period.

6.4.6. Electrocardiograms

12-lead ECG recordings (with subject in semi-recumbent position for 10 to 15 minutes before obtaining the ECG) will be performed in triplicate (approximately 10 minutes apart) at the time points specified in the Time and Events Table (Table 3). All ECGs will be performed **before** measurement of vital signs and collection of blood samples for laboratory testing.

6.4.7. Clinical Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 3, must be performed by the central laboratory, Quest Diagnostics Clinical Laboratory. Note: Screening T1DM auto-antibody tests may be carried out at local labs if results are required quickly, however a sample is to be sent to the central lab as well. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by Quest Diagnostics Clinical Laboratory. Reference ranges for all safety parameters will be provided to the site by Quest Diagnostics Clinical Laboratory.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), the results must be recorded in the subject's CRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Haematology, clinical chemistry, urinalysis, and other laboratory assessments are detailed below and will be collected at time points specified in the Time and Events Table (Table 3).

During visits when ECGs and vital signs are scheduled, blood samples will be collected after the completion of these assessments.

Haematology:

- Complete blood count with haemoglobin and other red blood cell indices, white blood cell count differential, and platelet count

Clinical Chemistry:

- Glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, ALT, AST, γ-glutamyltransferase, uric acid, magnesium, and phosphorus

Urinalysis:

- Specific gravity, pH, glucose, protein, blood by dipstick (if warranted, a microscopic evaluation will be completed)

Other urine tests at time points specified in the Time and Events Table:

- Urine pregnancy test (β human chorionic gonadotropin [β-HCG]) for female subjects of child bearing potential

- Urinary C-peptide and urinary creatinine as part of the MMTT (see Section 6.3.2.1)

Other blood tests at time points specified in the Time and Events Table:

- HbA1c

- C-peptide, glucose and glucagon as part of the MMTT (see Section 6.3.2.1)

- Triglycerides (fasting). No food or drink [except water] for at least 8 hours before sample collection. (Screening only)

- T1DM autoantibodies: - anti-GAD, anti-IA2, IAA

- Hepatitis B surface antigen (Screening only)

- Hepatitis C antibody. If hepatitis C antibody positive, RNA polymerase chain reaction should be performed on the same sample to confirm the result (Screening only)

6.4.7.1. Estimated Glomerular Filtration Rate

To ensure appropriate kidney function, eGFR will be calculated at Screening using the Modification of Diet in Renal Disease (MDRD) formula [Levey, 2009].

GFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)

6.4.8. Immunogenicity Sampling (Anti-albiglutide Antibodies)

Samples for immunogenicity testing will be obtained from all subjects before administration of the investigational product at Baseline and according to the schedule detailed in the Time and Events Table (Table 3).

The presence of anti-albiglutide antibodies will be assessed using a qualified enzyme-linked immunosorbent assay. The assay involves screening, confirmation, and titration steps (tiered-testing approach). Confirmed positive samples will be titrated to obtain the titre of antibodies and tested for GLP-1 and albumin cross-reactivity as well as for albiglutide neutralising activity. Samples positive for both anti-GLP-1 antibodies and drug neutralising antibodies may be tested for GLP-1 neutralising activity.

Additionally, in the case of systemic allergic reactions that include anaphylaxis, three 1-mL serum samples should be obtained at a time as close as possible to the event for albiglutide-specific IgE testing, and sent to the central laboratory for immediate distribution to the contracted testing laboratory (See SPM for details).

Further description of immunogenicity testing is in Appendix 3; instructions for sample processing are in the SPM.

6.4.9. Liver chemistry stopping and follow up criteria

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

liver chemistry stopping criteria 1-5 are defined below and are presented in a figure in Appendix 2 :

1. ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN and INR>1.5, if INR measured)

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥ 8xULN.
3. ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks

4. ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
5. ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for ≥2 weeks

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** withdraw investigational product for that subject
- Report the event to GSK **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN **and** INR>1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilise, or return to baseline values as described below.
- The subject may remain in the study as described in Section 4.4, however, investigational product must not be restarted

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilise or return to within baseline values

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilise or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety
- Can continue investigational product
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalise or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody
- Blood sample for PK analysis, obtained within 3 half-lives (15 days) of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product 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 SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.

- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

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

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).
- 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. **NOTE**: 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].
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease.

6.4.10. Adverse Events

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

6.4.10.1. Definition of an AE

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

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- 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.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, 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.

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

- 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
- 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

6.4.10.2. Definition of an SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires hospitalisation or prolongation of existing hospitalisation

   NOTE: In general, hospitalisation 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences

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

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise 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 hospitalisation, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

   NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.4.10.3. 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 Neutropaenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

6.4.11. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

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 are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

6.4.12. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias including atrial fibrillation/flutter (see Section 6.4.19).
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

6.4.13. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

6.4.14. Injection Site Reactions and Potential Systemic Allergic Reactions (e.g., rashes, urticaria, angioedema or anaphylaxis)

Adverse events broadly evaluated as injection site reactions have been reported in subjects treated with albiglutide (see IB for further information). . Manifestations were generally mild to moderate and included localized rash, itching, redness, or pain in the

area of the injection site. In some instances, reactions were noted to become more severe with subsequent injections. Injection site reactions should be reported as AEs or SAEs as appropriate and additional information on these events will be captured on specific eCRF pages.

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 reaction or other immune-medicated reactions (e.g., glomerulopathy, vasculitides, and hematologic abnormalities). 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 not attributable to another cause should have randomized study medication withdrawn and should **not** be rechallenged with albiglutide (see Section 4.4).

In the case of severe systemic allergic reactions that include anaphylaxis, angioedema, or other severe potential hypersensitivity reactions, three 1-mL serum samples should be obtained for immunogenicity testing and sent to the central laboratory (see details in the SPM) for immediate distribution to contracted testing facility for specific immunological testing (albiglutide-specific IgE and other antibody tests, as appropriate).

6.4.15. Pancreatitis

In clinical trials, acute pancreatitis has been reported in association with albiglutide and other glucagon-like peptide-1 (GLP-1) receptor agonists.

Subjects must be informed about the symptoms of pancreatitis in the subject information and instructed to contact the investigator immediately when they experience these symptoms. In the case of suspected pancreatitis, treatment with randomly assigned study medication should be withheld, and additional diagnostic measures (clinical examination, laboratory parameters, diagnostic imaging) must be initiated per routine clinical practice. If the suspected pancreatitis is confirmed, the subject must have investigational product stopped and not be rechallenged with study drug.

Detailed information on suspected pancreatitis events will be collected on special pages of the eCRF. Cases of suspected pancreatitis will be reviewed by an independent, blinded pancreatitis adjudication committee (Section 9.8).

6.4.16. Pancreatic Cancer

Recently, the FDA and the EMA independently undertook comprehensive evaluations of a safety signal arising from postmarketing reports of pancreatitis and pancreatic cancer in patients using incretin-based drugs [Egan, 2014]. These investigations, included examination of data from a 2013 research report revealing a possible pancreatic safety signal [Butler, 2013]. The FDA and EMA concluded that a causal relationship cannot be established currently but they will continue to investigate as more data become available.

As a result, events of pancreatic cancer occurring during the study will be carefully evaluated in addition to careful evaluation of malignancies more broadly given the interest in potential for malignancies when GLP-1R agonists are used in combination with insulin [EMA, 2014].

6.4.17. Medullary Thyroid Cancer

Safety concerns regarding thyroid C cell neoplasia were raised based on long term rodent studies with GLP-1R agonists. If a thyroid nodule is detected at either Screening or during the study, this should be evaluated in view of clinical practice guidance documents that have recently been published in the United States and Europe [Cooper, 2006; Pacini, 2006]. For example, the American Thyroid Association Guidelines Taskforce and the European Thyroid Cancer Taskforce both recommend that the initial evaluation of a thyroid nodule detected by physical examination may include an ultrasound of the neck and fine-needle aspiration, as warranted. Additional examinations may also be required based on the preliminary findings. The results of any investigation should be recorded in the relevant sections of the eCRFs. If medullary thyroid cancer is diagnosed, study drug should be withdrawn.

6.4.18. Pneumonia

In the Phase III program for albiglutide in T2DM, there was a higher incidence of pneumonia events with albiglutide compared with other comparators (refer to the IB for further information) and as such, cases of pneumonia occurring during the study will be monitored.

Detailed information on pneumonia will be collected on special pages of the eCRF.

6.4.19. Atrial Fibrillation/Atrial Flutter

In the Phase III program for albiglutide in T2DM, there was a higher incidence of atrial fibrillation/atrial flutter events with albiglutide compared with other comparators. These events were more common in subjects who were male, older or with renal impairment (refer to the IB for further information). Cases of atrial fibrillation or atrial flutter occurring during the study will be monitored.

Detailed information on atrial fibrillation and atrial flutter will be collected on special pages of the eCRF (see Section 6.4.12).

6.4.20. Pregnancy

Any pregnancy that occurs during study participation (i.e., from Baseline through to Week 64) must be reported using a clinical trial pregnancy form and investigational product withdrawn. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

6.4.21. Time Period and Frequency of Detecting AEs and SAEs

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

AEs (with the exception of hypoglycaemia and DKA events) will be collected from the start of study treatment and until the follow up contact. Hypoglycaemia SAEs and DKA SAEs will be collected from the time the subject consents until the follow-up contact and all other hypoglycaemia events will be collected from Week -2 until the follow-up contact.

SAEs (with the exception of hypoglycaemia and DKA SAEs as described above) will be collected over the same time period as stated above for AEs. However, any other SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, 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 reported to GSK within 24 hours, as indicated in Section 6.4.23.

6.4.22. Method of Detecting AEs and SAEs

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

"How are you feeling?"

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

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

6.4.23. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or death event	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Liver chemistry abnormalities				
ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN **and** INR>1.5, if INR measured)[1]	24 hours[2]	"SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable[3]	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents[3]

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists≥4 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥5xULN plus bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]

1. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.
2. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

.

For detailed descriptions of liver chemistry abnormalities, see Section 6.4.9.

The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

Procedures for documenting, transmitting and follow-up of medical device incidents along with the regulatory reporting requirements for medical devices are provided in the SPM.

6.4.23.1. Regulatory Reporting Requirements for SAEs

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

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

6.5. Pharmacokinetics

During the Treatment Period, sampling for PK assessments will occur at Visits 5 (Week 4) and 6 (Week 6); 2 samples will also be collected at any time after Visits 7 (Week 8) and 8 (Week 16). A total of 4 blood samples (2 mL each) will be obtained from each subject.

The samples collected at Visits 5 (Week 4) and 6 (Week 6) must be taken at least 2 days (48 hr) following the most recent dose of albiglutide/albiglutide matching placebo and may be taken at any time prior to the next dose. At Visit 6 (Week 6), or any subsequent visit where up or down titration of albiglutide/matching albiglutide placebo coincides with PK sampling, the PK sample must be taken prior to titration, such that it is taken no more than 16 hours prior to the subsequent dose.

The PK samples drawn at or any time after Visits 7 (Week 8) and 8 (Week 16) must be collected at least 2 days (48 hr) after a dose; however, the samples are not to be taken within 4 days of another sample.

All PK/PD samples will be processed according to instructions in the SPM and sent to the central laboratory for processing. It is critical that the actual sampling dates and times of PK sample collections are recorded accurately.

Plasma analysis will be performed under the control of GSK PTS-DMPK/Scinovo, the details of which will be included in the SPM. Concentrations of albiglutide will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SPM).

Once the plasma has been analysed for albiglutide any remaining plasma may be analysed for other compound-related metabolites and the results reported under a separate GSK PTS-DMPK protocol.

6.6. Pharmacogenetic Research

Information regarding pharmacogenetic (PGx) research is included in Appendix 1.

6.7. Biomarker Samples

Blood samples (serum samples and viable peripheral blood mononuclear cells (PBMC)) for exploratory biomarkers (see below) associated with autoimmune pathology will be collected at the time points indicated in the Time and Event Table (Table 3), frozen and stored.

After completion of the clinical trial and/or of any Interim Analysis, investigations may be performed on samples collected during the course of the trial to detect factors or profiles that correlate with other measures of response to treatment with albiglutide or with T1DM status. The results gained may also be of application for medically related conditions. Performance of these investigations will be conditional on the results of the clinical trial [principally, but not exclusively, on the primary measures of the clinical trial outcome] and samples may be selected for analysis on the basis of the clinical outcome.

Comparative examination of pre-dosing profiles of participants may uncover known or novel candidate biomarkers/profiles which could be used to predict response to treatment with albiglutide or provide new insights into T1DM and medically related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of albiglutide.

Exploratory biomarkers may include CD8-positive antigen-specific T-cells and biomarkers for β-cell death. If stored PBMCs are tested for CD8, samples will first be tested to see if they are HLA-A2 positive. The assay for β-cell death is based on DNA sequencing. As both of these assays require genetic testing, subjects will be asked to provide consent to give these samples. Refusing consent for these samples, will not prevent the subject from participating in the rest of the study.

Full details on sample collection, processing and shipment will be provided in the SPM/Quest manual.

All samples will be retained for a maximum of 15 years after the last subject completes the trial.

7. DATA MANAGEMENT

For this study subject data will be entered into GSK defined electronic case report forms (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 and an internal validated medication dictionary, GSKDrug. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

For this Phase II, randomised, multicentre, double blind, placebo controlled study, the primary objective is to evaluate the efficacy of albiglutide versus placebo on endogenous insulin secretion. The primary efficacy analysis endpoint will be change from baseline stimulated 2 hour MMTT C-peptide AUC at Week 52 following one year of treatment. Specifically, the treatment effect will be evaluated using the least squares means contrast relative to placebo. This contrast will be evaluated inferentially with a 2-sided t-test at the 0.05 criterion significance level.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

The study will randomly assign approximately 68 subjects to albiglutide+insulin group or placebo+insulin group in a 3:1 ratio, and allow for a 10% drop-out rate. Power is calculated for the primary efficacy analysis, comparing the change from baseline in stimulated 2 hour MMTT plasma C-peptide AUC (nmol/L) between albiglutide and placebo at 52 weeks.

Assumptions used in the power calculation are based upon results from the DEFEND-1 study [GlaxoSmithKline Document Number; 2011N125757_00].

- In the DEFEND-1 study, 91 subjects with a diagnosis of new-onset type 1 diabetes mellitus, aged 12-45 years, were enrolled to placebo+insulin group with similar inclusion/exclusion criteria and treated for 52 weeks. Among these placebo subjects, 53 of them were aged 18-30 years. The stimulated 2-hour MMTT C-peptide AUC change from baseline at Week 52 was -0.27 nmol/L. The corresponding observed standard deviation (SD) was 0.31 nmol/L. It is assumed that the SDs of 2 hour MMTT C-peptide AUC for the albiglutide and placebo groups in this study will be similar to the SD of the placebo group in DEFEND-1.
- As a conservative simplifying assumption, baseline was not included as a covariate. This is likely a less efficient analysis than if baseline was included as a covariate, and so the power estimate should be conservative.

With historical data from 53 placebo subjects in the DEFEND-1 study, a Bayesian approach will used for power and minimal detective treatment difference evaluation. Depending on the degree to which historical data will contribute to the placebo result of the current trial, at a two-sided significance level of 0.05, a sample size of 60 evaluable subjects (45 in the albiglutide group and 15 in the placebo group) provides 90% power to detect a treatment effect in the current study in the range from 0.19 nmol/L (using all the

information from the 53 placebo subjects from the DEFEND-1 study) to 0.30 nmol/L (not using any historical data). The corresponding minimal detectable difference will be 0.12 nmol/L to 0.18 nmol/L

8.2.2. Sample Size Sensitivity

Table 5 presents the study power for a combination of magnitudes of treatment effect size (rows) and various weight of historical data(%) (columns) and their contribution to the current placebo group. Table 6 presents the minimal detective difference under various weight of historical data. The greater the weight given to placebo data from the DEFEND-1 study, the greater the placebo effect from DEFEND-1 study will influence the placebo effect of the current study. Given that there are more placebo subjects in the DEFEND-1 study compared to the current study of 15 evaluable subjects, it is reasonable to assume DEFEND-1 placebo data contributes 50% of its placebo information. Sensitivity analyses will be done with low and high contribution rates.

Table 5 Power for DEFEND-1 in a 1-Sided 2-Sample t Test at the 0.05 Level

True Treatment Difference, (nmol/L)	Power (%) at a Sample Size of 60 With 3:1 Randomisation				
	Weight of historical placebo data				
	0	30%	50%	70%	100%
0.20	58%	78%	85%	89%	92%
0.22	66%	86%	91%	94%	96%
0.30	90%	99%	99%	100%	100%

Table 6 Minimal Detectable Difference

	Sample Size of 60 With 3:1 Randomisation				
	Weight of historical placebo data				
	0	30%	50%	70%	100%
Minimal Detectable Difference (nmol/L)	0.18	0.14	0.13	0.12	0.12

8.2.3. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

The intent-to-treat (ITT) population will include all randomly assigned subjects who receive at least 1 dose of study medication and who have at least 1 post-baseline assessment of the primary endpoint. ITT subjects will be analysed according to randomised treatment.

The safety population will include all enrolled subjects who receive at least 1 dose of study treatment. The safety population subjects will be analysed according to the treatment received.

Other analysis populations will be defined in the Reporting Analysis Plan (RAP).

8.3.2. Analysis Data Sets

Not applicable.

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

The primary comparison of interest is to demonstrate that the change from baseline in 2-hour MMTT plasma C-peptide AUC at Week 52 in the albiglutide group is significantly different from the placebo group. The hypothesis will be tested at the 5% significance level using a two-sided test. The primary comparison will be conducted using the ITT population.

8.3.3.2. Other Comparisons of Interest

The secondary and exploratory efficacy endpoints , and the safety endpoints will be compared between treatment groups as specified in the study objective sections. In general, comparisons of efficacy endpoints will use the ITT population and comparisons of safety endpoints will use the safety population as defined in Section 8.3.1.

8.3.4. Interim Analysis

No formal interim analyses are planned.

8.3.5. Key Elements of Analysis Plan

8.3.5.1. General Statistical Methods

Descriptive statistics will be presented for safety and efficacy endpoints. For continuous variables, descriptive statistics will include the mean, median, standard deviation, minimum, maximum, number of available observations, and number of missing

observations. For ordinal and nominal variables, descriptive statistics will include numbers and percentages for each score or category, number of available observations, and number of missing observations. Discrete numeric variables (counts) will be described through frequency counts (grouping counts as needed for clarity), mean, median, variance, minimum, maximum, number of available observations, and number of missing observations. Descriptive statistics will be provided for each treatment group. Complete data listings will be provided. Graphical displays will be presented when they add to understanding of the data.

Unless explicitly stated otherwise, results of hypothesis tests will be considered statistically significant if p values are less than or equal to 0.05, and will be deemed not significant if p values are greater than 0.05.

Statistical analyses will be performed with SAS, Version 9.1 or later, and R, Version 2.5.0 or later.

8.3.5.2. Subject Disposition and Demographic and Baseline Characteristics

Subject disposition, subject demographic and baseline characteristics will be summarised by treatment group and for both groups combined. Additional tabulations may be produced for various subgroups of subjects. Disposition, demographic characteristics, and other baseline characteristics will be listed by subject.

8.3.5.3. Efficacy Analyses

8.3.5.3.1. Primary Efficacy Analysis

The primary efficacy endpoint is change from baseline in 2 hour MMTT plasma C-peptide AUC at Week 52. The primary comparison is between this value in the albiglutide group and the placebo group, adjusting for baseline 2 hour MMTT plasma C-peptide AUC and age.

A mixed-effects model for change from baseline in 2 hour MMTT C-peptide AUC will be used to estimate and compare the albiglutide and placebo treatment effects at Week 52. Specifically, a repeated-measures mixed-effects model will be fitted with change from baseline 2 hour MMTT plasma C-peptide AUC as a dependant variable and baseline 2 hour MMTT C-peptide AUC, age group, treatment group, visit, and treatment group-by-visit interaction as independent variables. Historical placebo information with 50% weight will be incorporated into the mixed effect model by Baysian modelling using SAS PROC MCMC procedure. The mixed effects model will use a general (unstructured) covariance matrix as specification for the covariance among observations from the same subject.

A test of the treatment group difference at Week 52 will be provided by the comparison of the appropriate treatment group*visit least square means (Least square means).

The difference will be considered significant if the two-sided p-value for the comparison between treatments in change from baseline 2 hour MMTT C-peptide AUC is less than or equal to 0.05. The corresponding 95% confidence intervals will also be presented.

Subjects are scheduled to have on-therapy MMTTs performed at Week 16, 28, 52. Using a longitudinal repeated-measures model will provide an unbiased treatment difference estimate for the Week 52 time point, with better precision achieved by accounting for intra-subject variability than an analysis of covariance approach. In the event of missing observations at Week 52, the planned analysis and test are valid under a "missing at random (MAR)" assumption where missing data may depend on prior observations.

The above repeated mixed-effects model analysis will be repeated without placebo information from DEFEND1, and with 100% placebo information from the DEFEND 1 study as sensitivity analyses.

In addition to the t-tests described above, there will be a test for treatment group-by-time (continuous) interaction in the model (adjusted for baseline value and randomisation strata). A significant interaction would indicate that the treatment difference in 2 hour MMTT C-peptide AUC between groups varies over time to a greater degree than expected by chance. If there is no evidence of an interaction at the 0.05 level of significance, then the overall treatment group LS means (across all time points) will be reported.

Summary statistics for 2 hour MMTT C-peptide AUC and change from baseline will be tabulated by treatment group and assessment time for Week 16, 28, 52 and 64. Mean C-peptide AUC and mean change from baseline in C-peptide AUC will be plotted over time by treatment group.

An additional analysis of interest will be to examine the C-peptide AUC data for a trend over time. To assess this, a mixed-effects model will be specified with a linear trend after Week 28 to describe the mean rate of change (decrease) within treatment groups over time. To allow for an acute effect on C-peptide as observed in other studies, the baseline value will be entered as a covariate (not as one of the repeated measures over time); time will then be rescaled such that Time 0 is the first post-treatment C-peptide value, i.e., that at Week 16. The mixed-effects model will be specified with baseline C-peptide AUC, treatment group, and age as fixed effects. Between-subject differences in change from baseline AUC and treatment effect over time will be handled by specification of random effects for intercept and slope (time), respectively. The treatment group fixed effect will test the difference between groups in the mean intercepts (means at Week 16), and the treatment group-by-time interaction effect will test for differences between slopes over the period from Week 28 through Week 52. A general (unstructured) covariance matrix will be specified for the covariance among observations from the same subject.

8.3.5.3.2. Secondary Efficacy Analyses

Responder Analysis

The proportions of subjects meeting the definition of a responder will be compared between the albiglutide group and the placebo group at Week 4, Week 16, week 28, Week 52 and Week 64. A subject will be considered a responder if, at a given visit, the subject has:

- $HbA_{1c} \leq 7.0\%$ and
- Mean daily insulin use < 0.5 units/kg/day.

The proportion of responders will be analysed using descriptive statistics (frequency and percentage) by treatment group, and treatment comparisons will be undertaken with non-parametric, covariance-adjusted, extended Mantel-Haenszel tests .This technique is especially suited for situations in which covariance adjustment is needed to optimise statistical power, while minimising the modeling assumptions.

Percent of Subjects Achieving Partial Remission Status.

A subject achieving partial remission status is defined as a subject with Insulin Adjusted A1c (IDAA1C) ≤ 9 [Mortensen, 2009]. This secondary endpoint will be analysed in a similar method to the Responder analysis.

HbA1c.

This secondary efficacy analysis is to determine whether mean HbA_{1c} (adjusted for baseline HbA_{1c}, and age) is reduced in the albiglutide group compared to the placebo group at Week 4, Week 16, Week 28, Week 52 and Week 64.

HbA1c change from baseline will be analysed similarly to maximum stimulated plasma C-peptide using a mixed-effects model. 95% confidence intervals and the p-value for the treatment group differences at each time point of interest will be presented.

Exogenous Insulin Use.

This secondary efficacy analysis is to determine whether change in mean daily insulin use (adjusted for baseline daily insulin use and age) is reduced in the albiglutide group compared to the placebo group, at Week 4, Week 16, Week 28, Week 52 and Week 64. In this section, the term “mean daily insulin use” will refer to mean total daily insulin dose per kg body weight, which will be computed for each subject as the average of the total recorded daily insulin intake for at least three days, divided by the subject’s body weight in kg, using the most recently obtained weight measurement.

A similar mixed-effects model to that utilised for the maximum stimulated plasma C-peptide will be used to calculate the effects of albiglutide and placebo treatment on change from baseline mean daily insulin use.

The treatment group differences and 95% confidence intervals from repeated mixed-effects model at each time point of interest will be presented.

Subject-Reported Hypoglycaemic Events

Incidence of severe hypoglycaemia, documented symptomatic hypoglycaemia, and asymptomatic hypoglycaemia (as defined in Section 6.4.2) will be tabulated by treatment group. Incidence is defined as the numbers of subject-reported hypoglycaemic events per subject, and total percentages of subjects affected.

7- point glucose profile

Glucose level at each point will be summarised by treatment group at Baseline, Week 28 and Week 52. Number and magnitude of hypoglycaemic (<3.9 mmol/L) and hyperglycaemic excursions (> 10.0 mmol/L) from the 7-point glucose profile will also be reported at Baseline, Week 28 and Week 52.

72-hour CGM

Time spent with a plasma glucose <3.9 mmol/L, between 3.9 and 10.0 mmol/L, and >10.0 mmol/L will be summarised by treatment group at Baseline, Week 28 and Week 52.

8.3.5.3.3. Exploratory Analyses

Correlation between 120 minutes urinary C-peptide AUC and MMTT C-peptide AUC

Descriptive statistics for change from baseline in 120 minutes urinary C-peptide (corrected for urinary creatinine) AUC will be presented by treatment group and assessment time at Week16, Week 28, Week 52 and Week 64. The scatter plots of individual values of change in urine C-peptide AUC versus MITT C-peptide AUC will be presented for each treatment group and for both groups combined for Baseline, Week16, Week 28, Week 52 and Week 64.

Other Exploratory Endpoints

CD8-positive antigen specific T-cell responsiveness, and change from baseline in anti-GAD, anti-IA-2 and IAA antibody titres will be summarized at Week 4, Week 16, Week 28, Week 40, Week 52 and Week 64.

Change from baseline in global and domain scores in ADDQoL at 52 weeks will be compared between the albiglutide and placebo groups, between responders and non-responders and between subjects achieving partial remission status and subjects not achieving partial remission.

A model will be used to derive insulin secretion rates over the time course of glucose measurements by deconvolution of the observed C-peptide measurements associated with the prevailing glucose levels. Assessments will be made at Weeks -2 (baseline), 16, 28, 52 and 64. Changes from baseline between the albiglutide and placebo groups will be

compared, and also between responders and non-responders and between subjects achieving partial remission status and subjects not achieving partial remission.

The details of any further planned analyses will be provided in the RAP.

8.3.5.4. Safety Analyses

Subject demographics, medical history, prior and concomitant medications, vital sign measurements, laboratory values, ECG readings, physical examination assessments, and AE rates will be summarised 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. No inferential hypothesis testing will be performed on the safety variables. Some graphical summaries may be provided as well.

Adverse events will be coded using MedDRA. The coded events will be summarised by treatment group, in subsets of all treatment-emergent AEs, and all treatment-related AEs. Treatment-emergent AEs will be defined as any AEs, regardless of relationship to the investigational product, that occur after the first dose of the investigational product. Treatment-related AEs will be defined as any AEs that are considered by the investigator to be possibly, probably, or definitely related to the investigational product. In addition, the AE will be considered treatment related if relationship information is missing. Listings for the subsets of SAEs and treatment-related SAEs will be provided.

The number and percentage of subjects reporting specific events, such as nausea and vomiting, at each study week will be presented. Data for each week will include those subjects whose events started during that particular week, and also those with unresolved events from previous weeks. The incidence of specific events, such as nausea and vomiting, will also be plotted over time.

Further analysis details will be in the RAP.

8.3.5.5. Immunogenicity analyses

Anti-albiglutide antibody results will be analysed by treatment and by visit. The frequency of subjects positive for albiglutide-binding antibody and albiglutide-neutralising antibody, as well as those positive for GLP-1 and/or albumin cross-reacting antibodies, will be provided. Antibody titres for anti-drug antibody and Nab assays will be analysed by treatment and dose. Further exploratory analysis may be conducted dependent on the antibody response.

8.3.5.6. Pharmacokinetic Analyses

Albiglutide plasma concentrations and population PK parameters (e.g., CL/F, V/F, and Ka) will be summarised for the albiglutide group. The relationship between albiglutide PK parameters and patient covariates of interest will be evaluated graphically and in the population PK model.

8.3.5.7. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between plasma albiglutide concentrations and measures of glycaemic control (e.g., C-peptide, insulin use, HbA1c, etc) in the subject population will be explored, as data permit. The relationship between plasma albiglutide concentrations and other potential efficacy, tolerability (e.g., nausea and vomiting), and safety endpoints will be explored, as data permit.

8.3.5.8. Pharmacogenetic Analyses

See Appendix 1 for details about the Pharmacogenetics Analysis Plan.

8.3.5.9. Missing Data

Laboratory values below the level of quantification (BLQ) will be set to one-half the limit of quantification (unless noted otherwise) in computations for the aggregate analyses, but will be noted as BLQ in the listings. Laboratory values that are missing will be excluded from computations for the aggregate analyses and will be noted as missing in listings. On graphs, missing values will be shown by the absence of a data point.

The MMTT is expected to include assessments of C-peptide, glucose and glucagon at -10, 0, 15, 30, 60, 90, and 120 minutes, and AUCs are expected to be based on the assessments from Time 0 through 120 minutes. If one or more of these assessments is missing (note: values reported as BLQ are not considered missing), AUCs will be calculated based on the non-missing data using the trapezoidal rule. If the Time 0 assessment is missing, it will be substituted with the value from the -10 minute time point. For an AUC to be calculated, there must be a minimum of one fasting data point (assessments scheduled for -10 minutes and Time 0), and one post-mixed meal data point (assessments scheduled for 15, 30, 60, 90, and 120 minutes). If this minimum number of data points is not available, the AUC will be recorded as missing. If the MMTT is conducted when the plasma glucose values are out of the range specified, the data will not be included in the analysis and treated as missing.

The primary efficacy analysis employs a repeated-measures model using all follow-up values for all subjects (as described in Section 8.3.5.3.1). Under an MAR assumption where the missing data may depend on the prior observations, i.e., the conditional independence assumption, the model provides unbiased LSmean estimates for the treatment groups at the assessment time points.

If the amount of missing data is large, the potential impact of missing follow-up data on the conclusions of the primary analysis will be investigated through sensitivity analyses. For example, for each treatment group, the baseline characteristics of the subjects whose Week 52 mixed meal-stimulated C-peptide AUC is missing will be compared with those subjects with available Week 52 mixed meal-stimulated C-peptide AUC data to provide an assessment of the potential for the missing data to cause bias in the conclusions. The report will include presentation of the results of the sensitivity analysis, and a discussion of the implications of both the sensitivity analysis and the comparisons of baseline characteristics on interpreting the conclusions from the primary hypothesis test.

In analyses of HbA_{1c} and insulin usage, missing data at key analysis time points will be imputed using the last observation carried forward method.

8.3.5.10. Laboratory Values Below Limits of Quantification and Repeat Testing

Laboratory values below the level of quantification (BLQ) will be set to one-half the limit of quantification (unless noted otherwise) in computations for the aggregate analyses, but will be listed as BLQ in the listings.

If a laboratory test is repeated because of an apparent error, the repeat test result will be used in place of the original test result. Both the original test result and the repeat test result will be shown in the listings.

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

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

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.

Subject informed consent.

Investigator reporting requirements.

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

Before undergoing any Screening procedures, each subject will undergo the process of being fully informed about the study procedures and all associated risks and will then provide written and dated informed consent according to the regulatory and legal requirements of the participating country. The informed consent form must be approved by the IEC before it is given to any potential subject.

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

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Appendix 1, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, 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 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

The end of the study will be defined as when the last subject has their last visit.

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

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or 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 easily accessible 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 the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must 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. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that 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 results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

9.8. Pancreatitis Adjudication Committee

The pancreatitis adjudication committee composed of independent specialists in gastroenterology will review cases of possible pancreatitis. Details of this committee and case adjudication will be described a separate charter.

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11. APPENDICES

11.1. Appendix 1: Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) 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 PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	*HLA-B* 57:01 (Human Leukocyte Antigen B)*	Carriage of the *HLA-B*57:01* variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective *HLA-B*57:01* screening and exclusion of *HLA-B*57:01* positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective *HLA-B*57:01* screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. *HLA-B*57:01* screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	*HLA-B*15:02*	Independent studies indicated that patients of East Asian ancestry who carry *HLA-B*15:02* 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 *HLA-B*15:02* prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	*UGT1A1*28*	Variations in the *UGT1A1* 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 *UGT1A1* 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 *UGT1A1*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 PGx 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 PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to albiglutide.

Pharmacogenetic Research Objectives

The objective of the PGx 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 to albiglutide 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 PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx 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 or saliva samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

If taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (~6 ml) will be collected for the PGx 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 PGx research, but may be taken at any time while the subject is participating in the clinical study.

- The PGx 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 PGx 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 PGx 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 PGx sample, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx 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 the PGx 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 PGx 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 PGx 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.

Pharmacogenetics 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 PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx 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 the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarise the PGx 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 PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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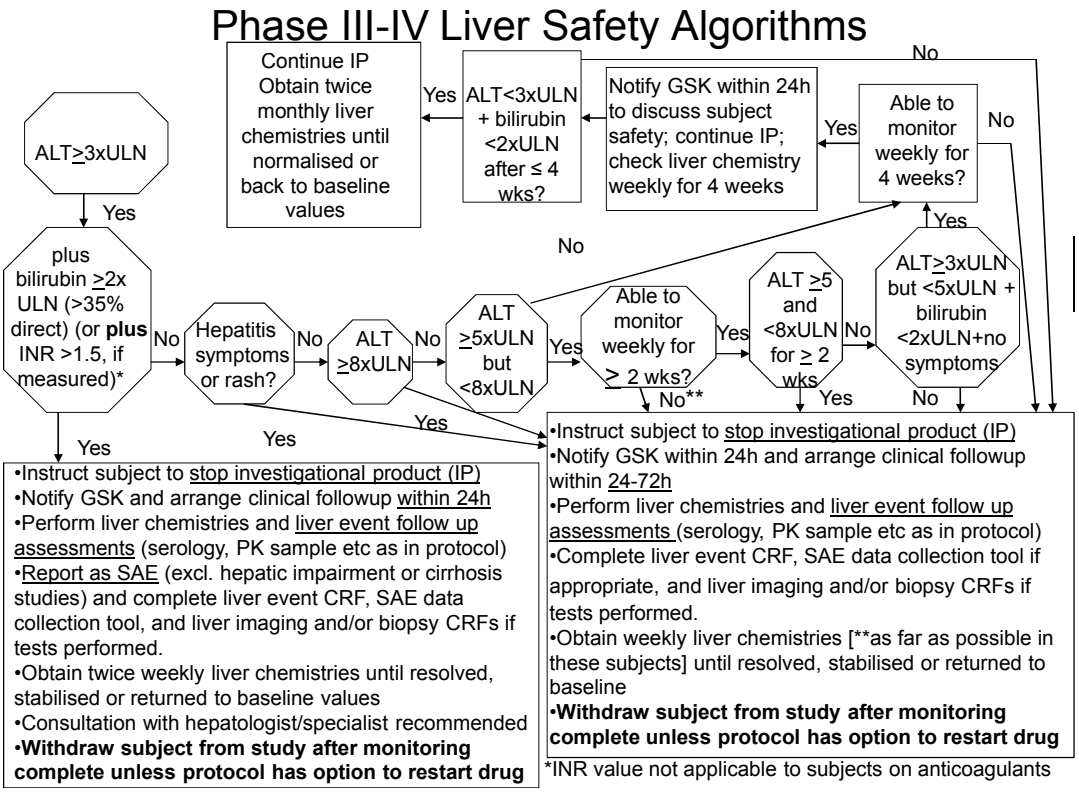
11.2. Appendix 2: Liver Chemistry Stopping and Follow-up Criteria



11.3. Appendix 3: Immunogenicity Testing

The immunogenicity of albiglutide will be evaluated by the following testing schemes and assays. Samples will be obtained from all subjects.

Sample Testing Schemes

Samples for immunogenicity testing will be obtained from all subjects before administration of the investigational product at Baseline and in accordance with the schedule in the Time and Events table.

The presence of anti-albiglutide antibodies will be assessed using a qualified screening enzyme-linked immunosorbent assay (ELISA). If serum samples contain anti-albiglutide antibodies, they will be further analysed for the specificity of antibodies by a confirmation assay. Confirmed positive samples will be titrated to obtain the titre of antibodies. To test whether the anti-albiglutide antibodies cross-react with endogenous glucagon-like peptide (GLP-1) and albumin, positive samples will be tested in anti-GLP-1 and anti-HA screening ELISAs. In addition, anti-albiglutide-positive samples will be tested in neutralisation antibody assays for neutralising activity against drug (albiglutide).

Antibody Detection Assays

The detection assays are ELISA based, which include screening, confirmation and titration assays (anti-HA is screening only). The procedures for the albiglutide immunoglobulin (Ig) (GAM) ELISA are described below:

1. 96-well ELISA plates are coated with albiglutide overnight.
2. Samples are diluted 1:50 and incubated on the blocked plates for 3 hours.
3. A horseradish peroxidase-labeled antihuman Ig (GAM) antibody is used as a detection antibody.
4. A tetramethylbenzidine substrate is used to produce the enzymatic reaction which is followed by an acid stop procedure.
5. The plates are read at 450 nm.
6. A positive control (positive control, normal serum pool spiked with anti-GLP-1 antibody) and negative control (negative control, pool normal human sera) are included on each assay plate.
7. Relative optical density values are calculated by dividing the mean optical density of sample or positive control by the mean optical density of the negative control.

Screening

Screening comprises determination of a cutoff value for drug-naïve type 1 diabetes mellitus subjects and identification of serum samples potentially positive for anti albiglutide antibody.

Confirmation

Specificity of serum antibodies is confirmed by competing their binding to albiglutide immobilised on plates with excess albiglutide in solution. If the sample is still positive after the confirmation assay, the sample will be reported as positive and further analysis will be done by the titration and neutralising antibody assays.

Titration

Confirmed positive samples (in confirmation) will be titrated to obtain a titre of anti-albiglutide antibody.

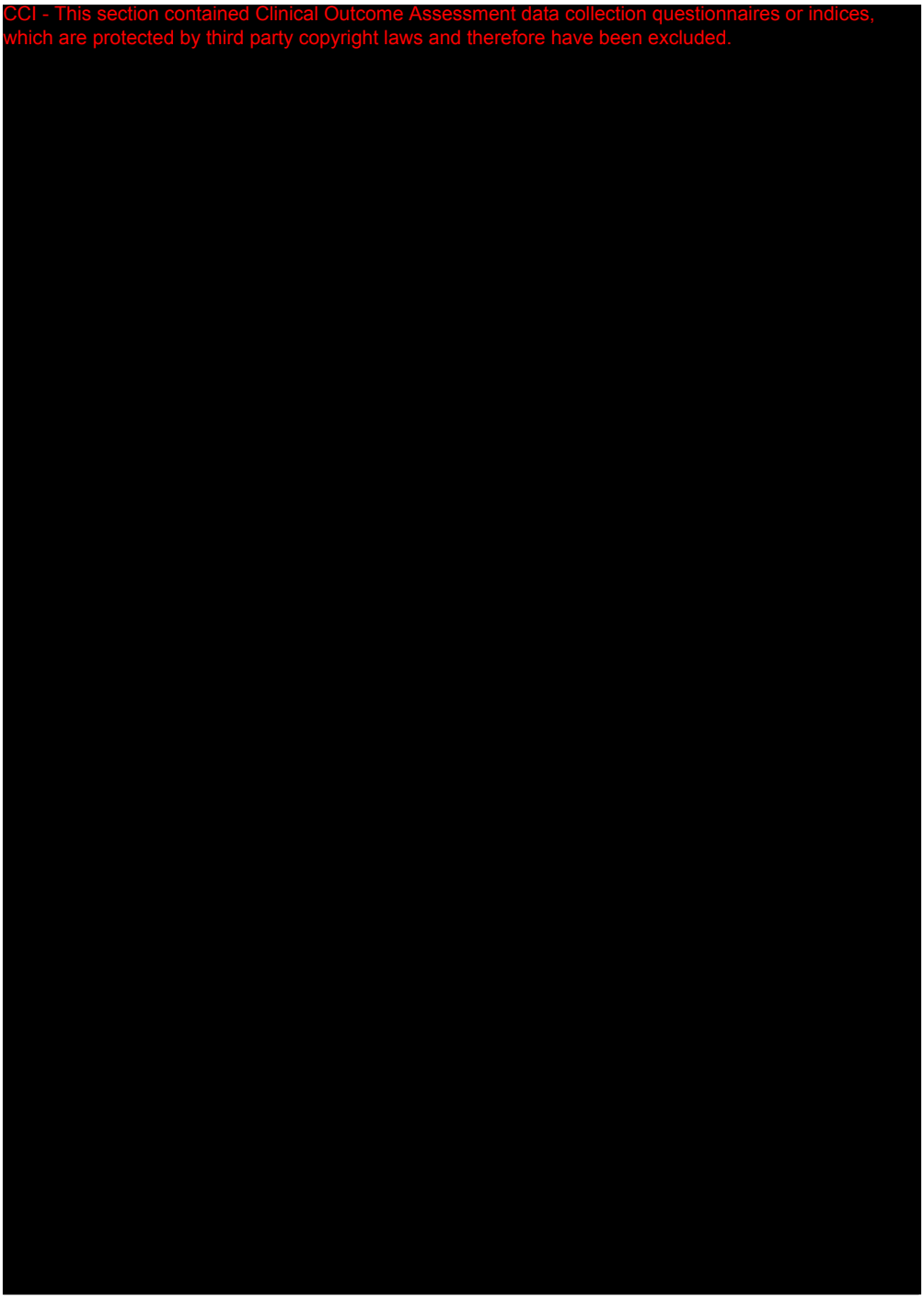
Neutralising Antibody Assays

The neutralising antibody assays are cell-based assays, which include screening, confirmation, and titration assays. Albiglutide-neutralising activity is measured by adding serum samples pre-incubated with a fixed concentration of albiglutide to GLP-1 receptor/CRE (cyclic adenosine monophosphate response element)-luciferase transfected cells and measuring luminescence intensity after 3 hours of incubation. Samples possessing neutralising activity will generate a reduced signal and will be further tested in the confirmation (specificity) assay if the generated signal is positive (i.e., below the assay's screening cutoff).

Immunogenicity Testing Report

The immunogenicity testing report will include the incidence of immunogenicity, incidence of neutralising antibodies, and the antibody titres (anti-drug antibody binding and neutralisation).

11.4. Appendix 4: Audit of Diabetes Dependent Quality of Life (AddQoL)



11.5. Appendix 5: Country Specific Requirements

Country-Specific Requirements

No country-specific requirements exist.

11.6. Appendix 6: Protocol Amendment Changes

11.6.1. Changes Resulting from Protocol Amendment 01

This amendment is applicable to all participating countries.

Summary of Changes

1. Update to SAE Contact information.
2. Correction of typographical error in Exclusion criterion 11.
3. Clarification wording added to the treatment compliance section to highlight that unused investigational product does not need to be returned at Week 2. There is no dispensing visit at Week 2 (as per Time and Events Table) so subjects may have been left without study medication until the next dispensing visit (Week 4).
4. Correction of footnotes 1 and 2 to Table 4 which had erroneously been transposed.
5. Clarification that insulin usage needs to be captured in the diary for at least 3 days prior to Baseline.

List of Specific Changes

Sponsor Information Page

Original text:

Sponsor Serious Adverse Events (SAE)* Contact Information:

GCSP Case Management Group
Telephone: PPD
e-mail address: PPD

*SAEs to be submitted via the eCRF. Please see Study Procedures Manual for details.

Amended Text:

Sponsor Serious Adverse Events (SAE)* Contact Information:

~~GCSP Case Management Group~~
~~Telephone:~~ PPD
~~e-mail address:~~ PPD

*SAEs to be submitted via the eCRF.

Please see Study Procedures Manual for details ***regarding submission of back-up paper SAE CRF pages.***

Section 4.3, Criterion 11

Original text:

Any clinically significant co-morbidity or abnormality (including psychiatric disorder, any other autoimmune endocrinopathy e.g., primary autoimmune hypothyroidism, hyperadrenalism, coeliac disease etc) that in the opinion of the Investigator, may pose additional risk in administering study medication or trial participation

Amended text:

Any clinically significant co-morbidity or abnormality (including psychiatric disorder, any other autoimmune endocrinopathy e.g., primary autoimmune hypothyroidism, ***hypo***adrenalism, coeliac disease etc) that in the opinion of the Investigator, may pose additional risk in administering study medication or trial participation

Section 5.5 Treatment Compliance, paragraph 1

Original text:

Investigational product accountability will be done for albiglutide/matching placebo at each study visit after the baseline visit through the end-of-treatment visit (at Week 52) inclusive. Subjects will be instructed to return all unused investigational product and used injector pens at each visit in order to perform drug accountability and determine compliance.

Amended Text:

Investigational product accountability will be done for albiglutide/matching placebo at each study visit after the baseline visit through the end-of-treatment visit (at Week 52) inclusive. Subjects will be instructed to return all unused investigational product and used injector pens at each visit ***(with the exception of Week 2 where only used injector pens need to be returned)*** in order to perform drug accountability and determine compliance.

Time and Events Table - Telephone calls, footnotes 1 and 2

Original Text:

Table 7 Time and Events Table – Telephone Calls

Study Procedure		Treatment (telephone calls to be performed as a minimum at the time points specified (± 3 days) and as required for appropriate management of the subject													
	Week	1[2]	3	5	7	9	10	11	12	13	14	15[1]	22[1]	34[1]	46[1]

1. Every 3-5 days during the first 2 weeks and for 2 weeks following study drug increase at Week 6
2. Telephone calls as necessary from Week 16 through to the end of the study to advise subjects on insulin dose adjustments, adverse event (AE) monitoring, hypoglycaemia and diabetic ketoacidosis monitoring

Amended text:

Table 8 Time and Events Table – Telephone Calls

Study Procedure		Treatment (telephone calls to be performed as a minimum at the time points specified (± 3 days) and as required for appropriate management of the subject													
	Week	1[1]	3	5	7	9	10	11	12	13	14	15[2]	22[2]	34[2]	46[2]

1. Every 3-5 days during the first 2 weeks and for 2 weeks following study drug increase at Week 6
2. Telephone calls as necessary from Week 16 through to the end of the study to advise subjects on insulin dose adjustments, adverse event (AE) monitoring, hypoglycaemia and diabetic ketoacidosis monitoring

Section 6.3.2.5, 2nd sentence

Original Text:

Subjects will record their daily insulin use in a diary. This information will be collected at Baseline, daily for the first 2 weeks and for at least 3 days preceding the telephone calls/visits at Week 3 through to Week 16, Week 22, Week 28, Week 34, Week 40, Week 46, Week 52 and Week 64.

Amended text:

Subjects will record their daily insulin use in a diary. This information will be collected ***for at least 3 days before*** ~~at~~ Baseline, daily for the first 2 weeks and for at least 3 days preceding the telephone calls/visits at Week 3 through to Week 16, Week 22, Week 28, Week 34, Week 40, Week 46, Week 52 and Week 64.

11.6.2. Changes Resulting from Protocol Amendment 02

This amendment is applicable to UK sites only.

SUMMARY OF CHANGES

Change to one of the acceptable methods of contraception at the request of the MHRA.

List of Specific Changes

Section 4.2. Inclusion criterion 6

Original text:

Male condom **combined with a female** diaphragm, either with or without a vaginal spermicide.

Amended Text:

Male condom **combined with a female** diaphragm, either with or without a vaginal spermicide. ***[UK only: this method of contraception is acceptable only if used with a vaginal spermicide].***