TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Repeat-dose Study in Subjects with Type 2 Diabetes Mellitus to Assess the Efficacy, Safety, Tolerability and Pharmacodynamics, of Albiglutide Liquid Drug Product

Compound Number: GSK716155

Development Phase: III

Effective Date: 26-MAY-2016

Protocol Amendment Number: 02

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N210004_00	2015-OCT-28	Original
2014N210004_01	2016-MAR-23	Amendment No. 1
Benefit risk table modified to provide further details relating to mitigation strategies. New text to clarify visit windows. Exclusion criteria related to abnormal TSH modified. Exclusion criteria numbering corrected. Exclusion criteria relating to positive urine drug screen result at Screening modified. Time and Event Table modified to add HbA1c sample at Week 12 Time and Event Table modified to remove the Week 13 PK sample and add a PK sample at Week 12. Details for collection of PK samples moved to SPM. Timings for handling of missing data changed.		
2014N210004_02	2016-MAY-26	Amendment No. 2
Protocol modified to allow subjects who discontinue investigational product to be followed for safety and efficacy unless the subject is "lost to follow-up" or withdraws consent. Minor updates to benefit risk table Clarification in inclusion criteria that those subjects on a stable dose of metforim must be receiving metformin as monotherapy. Exclusion criteria relating to use of dipeptidyl peptidase-IV inhibitors updated to include GLP 1 receptor agonists and other antidiabetic medications. Clarification of metformin dose adjustment. Text relating to prohibited medications modified to provide details on dipeptidyl peptidase-IV inhibitors, GLP 1 receptor agonists and other antidiabetic medications. Addition of visit windows to Time and Events Table. Footnotes to Time and Events Table updated Modifications made to the primary analysis, secondary analyses, supportive primary analyses, impact of missing data on primary analysis, and sensitivity analysis.		

Minor typographical errors

SPONSOR SIGNATORY

PPD

MAY-26-2016

Antonio. J. Nino M.D. Date

Physician Project Leader

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD MD PPD Pharmacovigilance	24-hour Safety Hotline PPD Email – N/A	24-hour Safety Hotline PPD PPD	PPD PPD	N/A
Secondary Medical Monitor	PPD MD PPD Pharmacovigilance	24-hour Safety Hotline PPD Email – N/A	24-hour Safety Hotline PPD PPD	PPD PPD	N/A
SAE Coordinator	PPD Pharmacovigilance North America	24-hour Safety Hotline PPD	24-hour Safety Hotline PPD PPD	PPD PPD	N/A
FAX number for SAE reporting				PPD PPD	

Sponsor Legal Registered Address:

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

PPD is the contract research organization for this study

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

Regulatory Agency Identifying Number(s): US IND 124228

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 2014N210004_02

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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1. PROTOCOL SYNOPSIS FOR STUDY 200952

Rationale

Albiglutide is a novel analogue of glucagon-like peptide-1 (GLP-1) with a sufficiently long half-life to permit once a week injection. Albiglutide has been developed for the treatment of type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies and has been approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and other regulatory agencies.

Currently, lyophilized albiglutide and the diluent are provided in a dual chamber cartridge (DCC), single-dose pen injector, requiring reconstitution prior to use. A liquid formulation of albiglutide will enable the commercialization of a liquid product in a single dose, ready-to-use prefilled syringe in an auto-injector. Study 201287, a healthy volunteer bioequivalence study will be conducted as the first component of the comparability assessment and the proposed study, Study 200952, will be conducted as the final component. This study will compare the efficacy, safety, tolerability and pharmacodynamic (PD) response of the lyophilized DCC pen injector product to the liquid auto-injector product. Specifically, potential for immunogenicity (e.g. incidences of anti-drug antibodies [ADA]) and injection site reactions (ISRs) will be evaluated.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the efficacy of albiglutide liquid product as measured by glycated hemoglobin (HbA_{1c}) change from baseline at Week 26.	• Change from baseline in HbA1c at Week 26
Secondary	
• To assess safety and tolerability of albiglutide specifically immunogenicity and ISRs.	• Adverse events (AEs) and serious AEs (SAEs), physical examinations, clinical laboratory evaluations, vital signs, and 12-lead electrocardiograms (ECGs). • Anti-albiglutide antibody production and rates of ISRs over time.
• To evaluate the PD effect of albiglutide on fasting plasma glucose (FPG) change from baseline at Week 26.	• Change from baseline in FPG at Week 26
• To assess the PD effect of albiglutide over time	• Change from baseline in HbA1c over time • Change from baseline in FPG over time
• To evaluate trough PK concentrations of albiglutide following repeat dosing	• Trough concentrations of albiglutide

Overall Design

- This is a phase III, randomized, double-blind, multicenter, parallel-group, repeat-dose, study of 26 weeks duration to evaluate the efficacy, safety, tolerability and PD response of albiglutide liquid drug product relative to the commercial lyophilized drug product in subjects with T2DM failing to achieve optimal glycemic control on their current regimen of diet and exercise or stable dose of metformin.
- At randomization, subjects will be stratified by age (<65 or ≥65 years of age), weight (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin).

Treatment Arms and Duration

- This study will comprise 3 study periods: screening (2 weeks), treatment (26 weeks) and for those subjects not entering the extension study a follow-up period (8 weeks).
- Subjects will be randomized in a 1:1 ratio to either:
  - Albiglutide active liquid auto-injector + placebo lyophilized DCC pen injector; or,
  - Albiglutide active lyophilized DCC pen injector + placebo liquid auto-injector.
- Study treatment will be administered once weekly by subcutaneous (s.c.) injection in the abdomen, thigh, or upper arm.
- Subjects will receive 30 mg of albiglutide for 4 weeks and will then be up-titrated to 50 mg albiglutide for the remaining 22 weeks of the study.

Type and Number of Subjects

- The study will recruit subjects with T2DM (>3 months since diagnosis) who are failing to achieve optimal glycemic control (HbA_{1c} 7-10%) on their current regimen of diet and exercise or stable dose of metformin (maintained for approximately 8 weeks prior to screening).
- Approximately 300 subjects will be randomized.

Analysis

Primary analyses:

HbA_{1c} change from baseline at Week 26 will be analyzed using a mixed-effect model with repeated measures (MMRM) in the intent-to-treat (ITT) population. MMRM will use all available data, including post-hyperglycemia rescue data, and will include data from subjects who discontinue treatment. Imputation under the non-inferiority null hypothesis for missing data will be incorporated. Non-inferiority testing will be performed at a one-sided alpha of 0.025 and non-inferiority margin of 0.4.

Secondary analyses:

The evaluation of the safety and tolerability as assessed by immunogenicity and ISRs of albiglutide liquid drug product and the lyophilized drug product will be provided by reporting the event rates, and the associated 95% CI.

The overall general safety and tolerability of albiglutide liquid drug product versus lyophilized drug product will be evaluated in tabular and/or graphical format and summarized descriptively.

The secondary endpoint FPG change from baseline at Week 26 will be analyzed using MMRM without imputation.

To assess the PD effect of albiglutide over time for the secondary endpoints change from baseline in HbA1c and in FPG over time MMRM models will be used.

PK trough plasma concentration data will be summarized by treatment.

2. INTRODUCTION

Albiglutide is a novel analogue of GLP-1 with a sufficiently long half-life to permit once a week injection. Albiglutide has been developed for the treatment of T2DM as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies.

2.1. Study Rationale

Currently, lyophilized albiglutide and the diluent are provided in a DCC, single-dose pen injector, requiring reconstitution prior to use. A liquid formulation of albiglutide will enable the commercialization of a liquid product in a single dose, ready-to-use prefilled syringe in an auto-injector. To support the development of the liquid auto-injector product, Study 201287, a healthy volunteer bioequivalence study will be conducted as the first component of the comparability assessment and the proposed study, Study 200952, will be conducted as the final component of the overall comparability assessment.

Extensive release and characterization testing has been utilized in studies to establish the comparability between samples of the liquid product and commercial lyophilized product. These studies were performed to evaluate the relevant differences in the quality attributes of the liquid and lyophilized products. However, non clinical studies are not suitable for predicting clinically relevant comparability of immunogenicity potential.

The albiglutide lyophilized products has been evaluated in an international program of studies involving approximately 9000 subject-years of overall exposure to date (including over 4000 subject-years of exposure to albiglutide) and has been found to have a favorable benefit:risk profile, including a low immunogenicity profile. In the clinical program with the lyophilized product, a low incidence (4.4%) of ADA was detected. Antibodies were non-neutralizing and mostly low titer and transient in nature. None of the antibodies impacted the pharmacokinetic (PK), PD or efficacy of the drug. There was a higher frequency of ISRs in antibody positive subjects, however most subjects with an ISR (including those ISRs classified as serious) were antibody negative. There was no apparent relationship between antibody positive status and other AEs that could be attributed to albiglutide.

This repeat-dose study in T2DM patients will determine if there are any clinically relevant differences between liquid drug product stored under recommended storage conditions to lyophilized drug product with respect to efficacy, safety, tolerability and PD response. Specifically, the immunogenicity potential (e.g., incidences of ADA) and ISRs will be evaluated as part of the overall safety assessment in this study.

2.2. Brief Background

Diabetes affects an estimated 347 million people worldwide, T2DM accounting for more than 90% of cases [World Health Organization, 2013]. The primary manifestation of this disease is chronic hyperglycemia, resulting from resistance to insulin action at a cellular and molecular level and a relative inadequacy in the secretion of endogenous insulin [American Diabetes Association, 2014]. Chronic hyperglycemia has been firmly established as a key factor in the development of microvascular complications

(retinopathy, nephropathy, and neuropathy) and to a lesser extent, macrovascular complications. The rapidly increasing incidence and prevalence of T2DM is a major worldwide healthcare issue due to increased patient morbidity and mortality and the costs associated with the management of these complications.

The management of glycemia in individuals with T2DM consists of diet, exercise, and weight reduction together with oral anti-diabetic drugs, injectable agents such as GLP-1 receptor agonists or insulin therapy, to achieve near normoglycemia as reflected by a target HbA_{1c} level of ≤7%, where possible, without significant hypoglycemia or other adverse effects of treatment. Despite the large number of available therapeutic agents, a high proportion of subjects fail to achieve or maintain target HbA_{1c} levels [Khunti, 2013] owing to the inexorable decline in endogenous insulin production characteristic of the disease, and limitations in existing treatments. New agents with complementary mechanisms (permitting combination use) or more favorable safety profiles are needed to help more subjects achieve glycemic targets.

Glucagon-like peptide-1 receptor agonists (e.g., exenatide, liraglutide, lixisenatide, dulaglutide) are therapeutic agents for the treatment of T2DM that stimulate insulin secretion in a glucose-dependent manner, suppress glucagon secretion with a low risk of hypoglycemia, delay gastric emptying, increase satiety, and are associated with modest weight reduction. The GLP-1R agonists lower FPG levels and reduce postprandial glucose excursions. In addition, in preclinical models GLP-1R agonists stimulated transcription of genes important for glucose-dependent insulin secretion and promoted β-cell neogenesis [Gautier, 2005].

Albiglutide is a novel analogue of GLP-1 generated through a genetic fusion of 2 modified recombinant human GLP-1 molecules linked in tandem to recombinant human albumin. Albiglutide is licensed for the treatment of T2DM as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies (oral antidiabetic therapies or basal insulin). It has been granted marketing authorization by the EMA (March 2014), the FDA (April 2014), Switzerland (Sep 2014) and Health Canada (2015). Details of the clinical trial results can be found in the Investigator Brochure (IB).

3. OBJECTIVE(S) AND ENDPOINT(S)

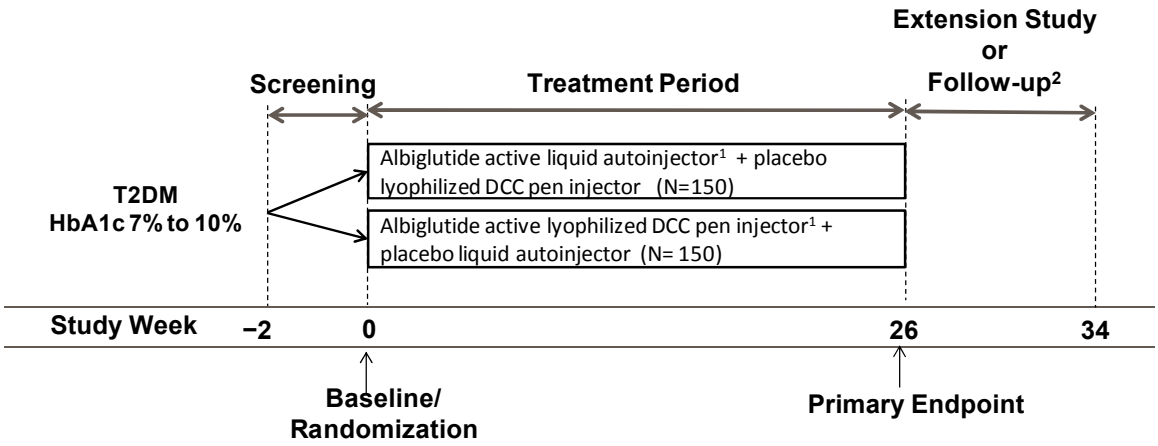
Objectives	Endpoints
Primary	
• To evaluate the efficacy of albiglutide liquid product as measured by glycated hemoglobin (HbA_{1c}) change from baseline at Week 26.	• Change from baseline in HbA1c at Week26
Secondary	
• To assess safety and tolerability of albiglutide specifically immunogenicity and ISRs.	• Adverse events (AEs) and serious AEs (SAEs), physical examinations, clinical laboratory evaluations, vital signs, and 12-lead electrocardiograms (ECGs). • Anti-albiglutide antibody production and rates of ISRs over time.
• To evaluate the PD effect of albiglutide on fasting plasma glucose (FPG) change from baseline at Week 26.	• Change from baseline in FPG at Week 26
• To assess the PD effect of albiglutide over time	• Change from baseline in HbA1c over time • Change from baseline in FPG over time
• To evaluate trough PK concentrations of albiglutide following repeat dosing	• Trough concentrations of albiglutide

4. STUDY DESIGN

4.1. Overall Design

- This is a phase III, randomized, double-blind, multicenter, parallel-group, repeat-dose, study of 26 weeks duration to evaluate the efficacy, safety, tolerability and PD response of albiglutide liquid drug product relative to the commercial lyophilized drug product.
- The study will recruit subjects with T2DM who are failing to achieve optimal glycemic control on their current regimen of diet and exercise or stable dose of metformin. Subjects will continue on their current regimen for the duration of their participation in the study.
- An overview of the study design is provided in Figure 1:

Figure 1 Study Schematic



DCC dual chamber glass cartridge

1. At baseline/randomization, albiglutide will be started at 30 mg once weekly with uptitration to albiglutide 50 mg once weekly at Week 4.
2. Follow-up visit only for those subjects who discontinued investigational product (see Section 5.5), were withdrawn from the study, or who have completed the 26 week treatment period, but do not consent and/or are not eligible to participate in the 26 week extension study (Study 204682).

- During the screening period, subjects will provide written informed consent and undergo procedures to determine eligibility for study participation. Screening will occur within 2 weeks of randomization. (Time and Events Table Section 7.1).
- At randomization, subjects will be stratified by age (<65 or ≥65 years of age), weight (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin).
- Subjects who completed the 26 week treatment period, did not discontinue investigational product, and meet all eligibility criteria may consent to participate in Study 204682, a 26 week extension study.

4.2. Treatment Arms and Duration

- This study will comprise 3 study periods (Figure 1): screening (2 weeks), treatment (26 weeks) and for those subjects not entering the extension study a follow-up period (8 weeks).
- Subjects will be randomized in a 1:1 ratio to either:
  - Albiglutide active liquid auto-injector + placebo lyophilized DCC pen injector; or,
  - Albiglutide active lyophilized DCC pen injector + placebo liquid auto-injector.
- Study treatment will be administered once weekly by s.c. injection in the abdomen, thigh, or upper arm.
- Study personnel will administer study treatment at clinic visits.

- Subjects will receive 30 mg of albiglutide for 4 weeks and will then be up-titrated to 50 mg albiglutide for the remaining 22 weeks of the study.
- Down-titration (dose reduction) of albiglutide from 50 mg to 30 mg is **NOT** permitted (see Section 4.4). If a subject experiences tolerability issues with the higher 50mg dose then the subject may discontinue investigational product (at the discretion of the investigator) and will be followed for safety and efficacy.
- During the study, any potential events of pancreatitis will be adjudicated by an independent pancreatitis adjudication committee (PAC) (Section 10.8).

4.3. Type and Number of Subjects

- The study will recruit subjects with T2DM (>3 months since diagnosis) who are failing to achieve optimal glycemic control (HbA_{1c} 7-10%) on their current regimen of diet and exercise or stable dose of metformin (maintained for approximately 8 weeks prior to screening).
- Approximately 300 subjects will be randomized.

4.4. Design Justification

Based on a review of data from Phase IIb and Phase III studies with the lyophilized albiglutide product a primary endpoint of 26 weeks was selected. In Phase IIb and Phase III studies the peak incidences of immunogenicity and titers were observed between 16 to 26 weeks of treatment. Therefore, the selected 26 week treatment duration should appropriately capture the rate of immunogenicity with the albiglutide liquid drug product. The treatment duration of 26 weeks will also allow for appropriate evaluation of glycemic control as measured by HbA_{1c} and FPG.

The current study is also applying the concept of design and objectives from the multiple-dose phase of Study GLP114856 which demonstrated the clinical comparability of Process 2 and Process 3 albiglutide lyophilized products in subjects with T2DM by showing that there were no clinically significant differences between Process 2 and Process 3 albiglutide lyophilized products with regards to safety and PD effects (i.e., HbA_{1c}, FPG) after 12 weeks of repeat dosing. To further strengthen the design, the current study is expanded by extending the repeat dosing period to 26 weeks and by adding the uptitration dosing scheme of 30 mg to 50 mg to allow for a comprehensive assessment of the efficacy, safety, tolerability and PD of the albiglutide liquid drug product and lyophilized drug product.

Subjects will receive 30 mg of albiglutide for 4 weeks and will then be up-titrated to 50 mg albiglutide for the remaining 22 weeks of the study. The intent of the dose titration scheme is to mimic real-world utilization of albiglutide as well as to maintain consistencies with what was done in the Phase III program. In the Phase III program, most studies used dose uptitration based on pre-specified glycemic criteria or clinical response. Based on the experience from pivotal Phase III studies for registration, the number of subjects withdrawing due to AEs or intolerance to albiglutide is expected to be low.

4.5. Dose Justification

Phase III studies confirmed the glycemic efficacy of both 30 mg and 50 mg doses of albiglutide lyophilized product, and both were generally well-tolerated. Although the 30 mg dose was effective at controlling glycemia for at least 2 years in many subjects with T2DM, an increase in dose to 50 mg weekly offered additional benefit without significant safety issues (See IB for further details).

In this study subjects will receive 30 mg of either albiglutide liquid drug product or albiglutide lyophilized drug product once weekly for 4 weeks and will then be up-titrated to 50 mg albiglutide for the remaining 22 weeks of the study.

4.6. Benefit:Risk Assessment

The following sections outline the risk assessment and mitigation strategy for this protocol which would apply to both the approved lyophilized drug product and the new liquid drug product in development.

Albiglutide lyophilized drug product has been evaluated in an international program of studies involving over 4000 subject-years of exposure to albiglutide. The program included 8 well-controlled Phase III studies ranging in duration from 32 weeks to 3 years, and using both 30 mg and 50 mg once weekly dosing. This has permitted a thorough assessment of efficacy, safety, and tolerability in a population of subjects with T2DM that spanned newly diagnosed individuals treated with diet and exercise alone through to subjects on background oral monotherapy, oral dual therapy, oral triple therapy, and basal insulin.

Summaries of findings from both clinical and non-clinical studies conducted with the albiglutide (GSK716155) lyophilized drug product can be found in the IB and in the product labeling for those countries where marketing authorization has been granted.

This is the first clinical investigation of the albiglutide liquid drug product in subjects with T2DM. A detailed description of the characteristics of the liquid product in the auto-injector device and results of nonclinical studies with this investigational drug product are presented in the IB Supplement.

Summary characteristics of the liquid formulation and the lyophilized formulation are shown in Table 1.

Table 1 Composition of Albiglutide (Liquid and Lyophilized for Injection, 30 mg/DCC and 50 mg/DCC)

Component	Liquid Albiglutide		Commercial Lyophilized Albiglutide	
	30 mg dose	50 mg dose	30 mg dose	50 mg dose
Injector type	***Pre-filled syringe with auto-injector***		***DCC in Pen injector***	
Final formulation pH	***5.9***		***7.0***	
Final albiglutide concentration	***50 mg/mL***		***60 mg/mL***	***100 mg/mL***
Injection volume	***0.6 mL***	***1.0 mL***	***0.5 mL***	

Stability data thus far suggest that the same product-related variants/impurity profiles are present in the liquid and commercial lyophilized products when stored at the recommended conditions. Based on the current understanding of albiglutide degradation pathways and clinical outcomes from exposure to variants/impurities; similar PK, PD, and clinical comparability between the liquid product and the lyophilized product is expected.

4.6.1. Risk Assessment

Key identified and potential risks associated with administration of albiglutide formulations in this study and mitigation strategies included in the protocol are summarized in Table 2. At this stage, the risk profile and associated pharmacovigilance and mitigation strategies are considered generally applicable to both the approved lyophilized product and the investigational liquid auto-injector. No risks specific to the liquid product have been identified in non-clinical studies to date. Mitigation strategies for this study have been incorporated for those risks (e.g. immunogenicity, ISRs) where a potential for differences between the formulations have been recognized.

Please also refer to the IB and any IB supplements as well as the complete Guidance for the Investigator and local approved product labeling.

Table 2 Risk Assessment for Albiglutide (GSK716155)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) (albiglutide [GSK716155]) Identified Risks		
Pancreatitis	Acute pancreatitis has been reported in association with albiglutide and other GLP-1 receptor agonists in clinical trials and during postmarketing experience. Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether they are at increased risk for pancreatitis.	Subjects with a history of acute or chronic pancreatitis are excluded from entering the study (See Section 5.2). Subjects will be informed of the characteristic symptom of pancreatitis: persistent severe abdominal pain. If pancreatitis is suspected, albiglutide should be promptly discontinued and if pancreatitis is confirmed, study treatment will not be restarted (see Section 5.5). Risk communication via guidance for investigators (see albiglutide IB) and informed consent form for subjects.
Gastrointestinal (GI) events.	Albiglutide has not been studied in subjects with severe GI disease, including severe gastroparesis. Use of albiglutide can be associated with GI side effects such as diarrhea, nausea, and vomiting.	Subjects with severe gastroparesis are excluded from entering the study (See Section 5.2). Subjects with a history of significant GI surgery that in the opinion of the investigator is likely to significantly affect upper GI or pancreatic function are excluded from entering the study (See Section 5.2). Risk communication via guidance for investigators (see albiglutide IB) and informed consent form for subjects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypoglycemia.	Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycemia when used as monotherapy or in combination with agents such as metformin which also have low intrinsic risk for significant hypoglycemia.	To reduce the risk of hypoglycemia when starting albiglutide all subjects are required to have HbA1c ≥7.0 at screening (see Section 5.1). Subjects are neither allowed to use insulin nor insulin secretagogues during the study except as part of hyperglycemia rescue (see Section 5.4) Risk communication via guidance for investigators (see the albiglutide IB) and informed consent form for subjects.
Immunogenicity (e.g., including anti-drug antibodies, clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, and other potential immune-related AEs).	Risk assessment of the albiglutide molecule predicted low immunogenic potential, which was substantiated for the commercial lyophilized DCC pen injector product in the registration program. Treatment-emergent anti-drug antibodies were detected in ~5% subjects over studies of up to 3 years duration and were generally transient, of low titer, and not neutralizing. Subjects who tested positive for anti-albiglutide antibodies experienced a similar glycemic response (HbA1c and fasting plasma glucose) to those who did not test positive for antibodies. Other than injection site reactions (see below), the overall safety profile appeared similar among the subset of subjects who did and those who did not test positive for anti-albiglutide antibodies. Changes in the propensity of the liquid product to form aggregates could have an impact on anti-drug antibody characteristics or immune related AEs. However, the likelihood of clinically important changes in anti-drug antibody characteristics or immune related AEs with the liquid albiglutide drug product compared to the lyophilized drug product is considered low based on the absence of substantive qualitative differences between formulations.	A pre-exposure baseline serum sample will be taken and tested for pre-existing ADAs. The development of anti-albiglutide antibodies will be assessed as part of this study. Risk communication via guidance for investigators (see albiglutide IB) and informed consent form for the subject.
Hypersensitivity Reactions	Systemic allergic/hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III program with lyophilized albiglutide. Data	Subjects with a known allergy to albiglutide or any product components (including yeast and human albumin) are

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	have not demonstrated an association of albiglutide with an increased incidence of anaphylaxis, angioedema, or urticaria. However, there was one non-serious hypersensitivity event (rash and itching associated with dyspnea upon rechallenge) that was consistent with a possible albiglutide-related systemic hypersensitivity reaction in a female subject who was anti-albiglutide antibody negative. See albiglutide IB.	excluded from the study (See Section 5.2). Subjects will be informed of the symptoms of severe hypersensitivity or allergy and be advised to seek medical assistance immediately. Risk communication via guidance for investigators (see albiglutide IB) and informed consent form for subjects.
Injection site reactions (ISRs)	Albiglutide injections may cause rash, erythema or itching and/or other reactions at the site of injection. In the Phase III program with the lyophilized drug product, most subjects with ISRs did not test positive for anti-albiglutide antibodies. However, injection site reactions were reported more frequently among those who did test positive for anti-albiglutide antibodies (41% of the ADA positive subjects reported one or more injection site reactions) than among those who were consistently antibody negative (14% of the antidrug antibody negative subjects reported one or more injection site reactions). Overall, for albiglutide, injection site reactions have not been associated with clinically significant sequelae; although they can be a tolerability issue and were the most common reason for withdrawal of study medication for subjects (approximately 2.0%) in the albiglutide group. Differences between formulation characteristics (e.g. lower pH and larger volume for the 50 mg dose of the liquid formulation) may impact the injection site reaction profile.	Subjects will be advised that when injecting in the same region, to use a different injection site each week. Risk communication via guidance for investigators (see albiglutide IB)) and informed consent form for subjects. The development of injection site reactions will be assessed as part of this study where the investigator or designee will administer both the albiglutide liquid drug product and the albiglutide lyophilized drug product.
Other adverse reactions (e.g., pneumonia, atrial fibrillation/atrial flutter, and appendicitis)	In the Phase III program in T2DM, other possible albiglutide related adverse reactions were identified. These events occurred at a cumulative incidence <3% in studies up to 3 years in duration. These events were reported more frequently with albiglutide than comparators. See albiglutide IB.	Risk communication via guidance for investigators (see albiglutide IB) and informed consent form for subjects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) (albiglutide [GSK716155]) Potential Risks		
Thyroid C-cell tumors	GLP-1 receptor agonists, including albiglutide increase serum calcitonin in rodents and other GLP-1 receptor agonists are associated with thyroid C-cell focal hyperplasia and C-cell tumors in rodents It is unknown whether GLP-1 receptor agonists are associated with thyroid C-cell tumors in humans, including medullary thyroid cancer (MTC).	Subjects with a personal or family history of MTC or subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) are excluded from the study (See Section 5.2). Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. Routine monitoring of serum calcitonin is not recommended. However, if serum calcitonin is found to be elevated the subject should be referred to a specialist for further evaluation. If MTC or other thyroid C-cell neoplasia is diagnosed, study treatment will be discontinued (see Section 5.5).
Other malignant neoplasms	Theoretical concerns have been raised regarding use of incretin based therapies and other malignancies such as pancreatic cancer [Egan, 2014] and malignancy when used in combination with insulin based on hypotheses of biological plausibility [European Public Assessment Report, 2014], and hematological malignancies [FDA Summary Basis of Approval, 2014].	Relevant data on pancreatic cancer are summarized in the albiglutide IB. Subjects with a history of cancer that has not been in full remission for at least 3 years before screening are excluded from the study (See Section 5.2). A history of squamous cell or basal cell carcinoma of the skin or treated cervical intra-epithelial neoplasia I or II is allowed.
Cardiovascular (CV) safety of antidiabetic therapy	T2DM is associated with an elevated risk of CV disease. Global regulatory agencies require new antidiabetic therapies to demonstrate that the new therapy is not associated with an unacceptable increase in CV risk. In the Phase III registration program, an independent Clinical Endpoint Committee prospectively adjudicated blinded CV events. The final CV meta-analysis showed no increased CV risk (MACE [major adverse cardiovascular event] + composed of CV death, myocardial infarction [MI], stroke, and hospitalization for unstable angina) with albiglutide versus all comparators (MACE+ hazard ratio =	Relevant data on cardiovascular events are summarized in the albiglutide IB. Subjects with clinically significant CV and/or cerebrovascular disease within 3 months before screening will be excluded from the study. Further details are provided in Section 5.2

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	1.00; 95% CI: 0.68, 1.49). See Section 5.4 of the IB.	
Hepatotoxicity	Hepatotoxicity is an area of interest in drug development. Patients with T2DM are at increased risk for liver enzyme abnormalities and disease related liver conditions. One subject treated with albiglutide in the Phase III clinical program developed probable drug induced liver injury with an asymptomatic elevation in alanine amino transferase (ALT) and total bilirubin although the cases had some atypical features and complicating factors .	Routine liver safety laboratory evaluations will be conducted and specific withdrawal criteria for elevated liver function tests have been defined (See Section 5.5.4).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) (albiglutide [GSK716155]) Additional Considerations		
Subject population with severe renal impairment (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2)	Experience in T2DM subjects with severe renal impairment is limited (in the Phase III programme a total of 19 subjects with eGFR <30 mL/min/1.73m^2 received albiglutide). In a Phase III study of patients with varying degrees of renal impairment, in the albiglutide group, on-therapy GI AEs occurred with a higher incidence and higher event rate in subjects with moderate and severe renal impairment compared to those with mild renal impairment. GI events may lead to dehydration and worsen renal function.	Subjects with an eGFR ≤30 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease (MDRD) formula) are excluded from the study (see Section 5.2). Risk communication via guidance for investigators (see the albiglutide IB) and informed consent form for subjects.
Drug interactions	Albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the development program, drug interactions studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant PK or PD effects.	Investigators will be advised to take the effect of albiglutide on gastric emptying into account when prescribing concomitant medication.
Fetal & neonatal developmental toxicity	Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Albiglutide administration during the major period of organogenesis in female mice resulted in embryofetal lethality, and bent/wavy ribs in the fetus at 50 mg/kg/day. Offspring of mice dosed with 50 mg/kg/day during organogenesis had reduced pre-weaning body weight (which recovered after weaning), dehydration and coldness, and a delay in balanopreputial separation. Given that albiglutide is an albumin-based protein therapeutic, it is likely to be transferred to breast milk. Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation.	Subjects who are breastfeeding, pregnant or planning a pregnancy during the course of the study are excluded. Additionally, all females of child-bearing potential must be taking adequate contraception during the study and have a negative pregnancy test prior to entry. See Section 5.1 for further details. Risk communication via guidance for investigators (see IB) and informed consent form for subjects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Accelerated sexual maturation in juveniles	Long-acting GLP-1R agonists have the potential to accelerate sexual maturation in monkeys based on absolute testes weight and similar trends in prostate, seminal vesicle, epididymides weights and histological assessment of maturity.	Subjects under 18 years of age are excluded (see Section 5.1).
Study Procedures		
Albiglutide matching placebo injections	Albiglutide placebo injections using the lyophilized DCC pen injector were associated with a clinically relevant rate of injection site reactions in the Phase III studies. There is no experience with placebo injections using the liquid auto-injector, including volume and pH differences from the lyophilized product placebo.	Subjects will be advised that when injecting in the same region, to use a different injection site each week. Risk communication via informed consent form for subjects.

4.6.2. Benefit Assessment

In subjects with T2DM treatment with albiglutide lyophilized drug product resulted in clinically relevant lowering of HbA_{1c} at both the 30 mg and 50 mg doses when given as monotherapy and in combination with metformin, sulfonylureas (SUs), thiazolidinedione or basal insulin. The durability of the effect on glycemic control was shown over a study period of up to 3 years. Consistent with its mechanism of action, albiglutide was not associated with clinically relevant hypoglycemia except when used in combination with an SU or insulin, and incidence rates with the combination were less than those reported with SUs or insulin alone. Body weight decreased slightly or remained stable during treatment, which is of benefit considering that continuous weight gain is a clinical problem in this patient group. Maintaining body weight while decreasing HbA_{1c} is therefore considered a beneficial effect of importance.

There are no clinical data available for the use of the albiglutide liquid drug product in humans. Based on the understanding of albiglutide degradation pathways and clinical outcomes from exposure to variants/impurities clinical comparability between the liquid drug product and lyophilized drug products is expected.

4.6.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the known and potential risks identified with albiglutide are justified by the benefits demonstrated in subjects with T2DM.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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

5.1. Inclusion Criteria

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

[1] AGE
1. Aged 18 to 80 years of age inclusive, at the time of signing the informed consent.

[2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Historical diagnosis of T2DM (at least 3 months), experiencing inadequate glycemic control on current regimen of diet and exercise or on a stable dose of metformin of at least 1500 mg or the documented maximal tolerated dose if less than 1500 mg metformin (monotherapy), maintained for approximately 8 weeks prior to screening
3. HbA_{1c} ≥7.0% and ≤10%. If the first screening HbA_{1c} does not meet the eligibility criterion, the HbA_{1c} value may be checked up to 2 times during screening, and if the average of these determinations meets the criterion, the subject can be randomly assigned to treatment.
4. Hemoglobin ≥11 g/dL (≥110 g/L) for males and ≥10 g/dL (≥100 g/L) for females.

[3] WEIGHT
5. Body mass index ≤40 kg/m^2.

[4] SEX
6. Male or female
7. Female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test for females of reproductive potential only), not breastfeeding, and at least one of the following

conditions applies:

a) Reproductive potential and agrees to follow one of the options listed in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (eg., combined oral contraceptive pill; see Appendix 2) from 30 days prior to the first dose of study medication and until after the last dose of study medication and completion of the follow-up visit.

- This does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent. Other situations in which contraception in FRP may not need to be mandated should be discussed with the Medical Monitor.

b) Non-reproductive potential defined as either:

- Pre-menopausal with one of the following: (i) documented tubal ligation; (ii) documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion; (iii) hysterectomy; or (iv) documented bilateral oophorectomy, or;
- Postmenopausal defined as 12 months of spontaneous amenorrhea and age appropriate (i.e., >50 years). In questionable cases, a blood sample with simultaneous follicle stimulating hormone (FSH) >40 mIU/mL and estradiol <40 pg/mL (<140 pmol/L) is confirmatory, depending on local laboratory ranges. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

[5] INFORMED CONSENT
8. Able and willing to provide informed consent.

5.2. Exclusion Criteria

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

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Type 1 diabetes mellitus
2. 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 intra-epithelial neoplasia I or II is allowed).
3. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.
4. History of acute or chronic pancreatitis.
5. Abnormal (i.e., outside the normal reference range) thyroid stimulating hormone

(TSH) at screening.

6. Severe gastroparesis, i.e., requiring regular therapy within 6 months before screening.
7. History of significant GI surgery that in the opinion of the investigator is likely to significantly affect upper GI 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 GI function).
8. History of severe hypoglycemia unawareness (i.e., the absence of autonomic warning symptoms before the development of neuroglycopenic symptoms such as blurred vision, difficulty speaking, feeling faint, difficulty thinking, and confusion)..
9. Diabetic complications (e.g., active proliferative retinopathy or severe diabetic neuropathy) or any other clinically significant abnormality (including a psychiatric disorder) that, in the opinion of the investigator, may pose additional risk in administering the investigational product.
10. Clinically significant CV and/or cerebrovascular disease within 3 months before screening including, but not limited to, the following:
    - Stroke or transient ischemic attack.
    - Acute coronary syndrome (MI or unstable angina not responsive to nitroglycerin).
    - Cardiac surgery or percutaneous coronary procedure.
    - Current or history of heart failure (New York Heart Association class III or IV).
11. QTcF > 470 msec, where QTcF is the QT interval corrected for heart rate according to Fridericia's formula.
12. ALT >2.5xULN or bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
13. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

    NOTES:

    - Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.
    - Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria.
14. eGFR ≤30 mL/min/1.73 m^2 (calculated using the MDRD formula) at screening.

    Note: The use of metformin in subjects with varying degrees of renal function should be in accordance with the metformin product label.

15. Hemoglobinopathy that may affect proper interpretation of HbA_{1c}.
16. Medical or psychiatric disorders that would preclude effective participation in study.

[2] CONCOMITANT MEDICATIONS (see Section 6.10)

17. Use of oral or systemically injected glucocorticoids within the 3 months before randomization or high likelihood of a requirement for prolonged treatment (>1 week) in the 6 months following randomization. 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, epidural, and topical corticosteroids are allowed.
18. Use of GLP 1 receptor agonists at any time. Use of dipeptidyl peptidase-IV inhibitors within the 3 months before randomization. Use of any other antidiabetic medications with the exception of metformin within 3 weeks before randomization.

[3] RELEVANT HABITS

19. History of alcohol or substance abuse within one year before screening.

[4] CONTRAINDICATIONS

20. Known allergy to albiglutide or any product components (including yeast and human albumin), any other GLP-1 analogue, or other study medication's excipients OR other contraindications (per the prescribing information) for the use of potential study medications.

[5] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

21. Positive urine alcohol/drug screen result at Screening, unless the subject is taking a medically approved medication for which a positive drug screen simply verifies the use of this medication
22. A positive test for human immunodeficiency virus (HIV) antibody.
23. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
24. Fasting triglyceride level >750 mg/dL at screening.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. 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 is required including demography, screen failure details, eligibility criteria, and any SAEs.

- Re-screening of subjects who did not meet the eligibility criteria for HbA_{1c} (≥7.0% and ≤10%) is permitted. If the first screening HbA_{1c} does not meet the eligibility criterion, the HbA_{1c} value may be checked two further times during the screening period, and if the average of these determinations meets the entry criterion, the subject can be randomized.

5.4. Hyperglycemia Rescue

During the study of diabetics, there is always the possibility of hyperglycemia, which might impact subject safety. After randomization, subjects who experience persistent hyperglycemia will qualify to undergo hyperglycemia rescue. Investigators must adhere to the labeling of the US FDA-approved prescribing information or to the local labeling of the respective country for all rescue medications. The conditions for hyperglycemia rescue are defined in Table 3.

Table 3 Conditions for Hyperglycemia Rescue

Time Interval on Treatment	Hyperglycemia Rescue
≥Day 1 and <Week 2	No rescue
≥Week 2 and <Week 4	FPG ≥280 mg/dL1
≥Week 4 and <Week 12	FPG ≥250 mg/dL1
≥Week 12 and <Week 26	HbA1c ≥8.5% and ≤0.5% reduction from Baseline

1. Confirmed by a second sample drawn within 7 days analyzed by the central laboratory

Subjects can be rescued at any time on or after Week 2. Subjects who qualify should return to the study center at the next scheduled weekly visit for rescue. The efficacy assessments should be obtained if these assessments are not included as part of the regular scheduled visit. As determined by the investigator, rescued subjects may be seen more frequently during unscheduled visits until their diabetes has stabilized. Subjects will continue in the study after rescue and will continue with their blinded study treatment until the study is completed. It is critical that subjects continue in the study after rescue in order to have complete and unbiased follow-up of long-term safety and efficacy assessments.

The rescue criteria above should apply in the majority of circumstances; however, in the event a subject experiences significant evidence of hyperglycemia (e.g., symptoms of polyuria and polydipsia and laboratory evidence of hyperglycemia), the investigator may, based upon his or her judgment, rescue the subject with appropriate therapy at any time following randomization. Such subjects may either have rescue medication added to the

existing randomly assigned study medication or, if in the judgment of the investigator (or the product labeling for rescue medications) this is not appropriate, the subject will be discontinued from randomly assigned study medication and appropriate rescue therapy initiated. Such subjects will continue to be followed in the study for their safety information; however, they will not receive further randomly assigned study medication. Rather they will be prescribed alternative therapy in order to optimize their diabetes control.

The preferred postrescue add-on treatment is insulin. Other medications may be added at the investigator's discretion. The addition of other GLP-1 analogues (exenatide or liraglutide) is prohibited as the safety of dosing with multiple GLP-1 analogues is unknown. The use of dipeptidyl peptidase-IV inhibitors is prohibited. The addition of a thiazolidinedione (rosiglitazone or pioglitazone) is discouraged.

5.5. Withdrawal/Stopping Criteria

Every effort should be made to keep subjects in the study. The reason for a subject discontinuing investigational product or withdrawing from the study will be recorded in the subject's electronic case report form (eCRF).

5.5.1. Permanent Discontinuation of Investigational Product

A subject may permanently discontinue investigational product at any time at his/her own request, or at the discretion of the investigator for safety or compliance reasons. A subject must permanently discontinue investigational product for the pre-specified reasons below.

- Any AE, which, in the opinion of the investigator precludes effective participation of the subject or poses a safety concern
- The following AEs **will** require discontinuation from investigational product:
    - Confirmed pancreatitis, acute or chronic.
    - Pancreatic cancer.
    - Confirmed MTC or other thyroid C-cell neoplasia.
    - Liver chemistry abnormalities exceeding the threshold criteria outlined in Section 5.5.4
    - QTc abnormalities exceeding the threshold criteria outlined in Section 5.5.5.
    - Severe allergic/hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology.
- eGFR $\leq$30 mL/min/1.73 m^2 (calculated using the MDRD formula).
- Subject becomes pregnant or intends to become pregnant during the study.
- Need for chronic use of a prohibited concomitant medication (Section 6.10.2)

- Major protocol deviation (the investigator should discuss the protocol deviation with the medical monitor before withdrawing study medication)
- Subject decision (reason to be documented in the eCRF, if specified by the subject)
- Investigator discretion
- Study closed/terminated or investigator site closed (where subject transfer to another site is not possible)

In all cases, the reasons for investigational product discontinuation and the date of the last dose will be recorded in the subject's electronic case report form (eCRF) and the subject will continue in the study as described in 5.5.1

5.5.1.1. Procedures for Subject Follow-up Following Discontinuation of Investigational Product

Subjects will be educated on the importance of remaining in the study and attending all scheduled study visits.

Subjects who permanently discontinue investigational product will be expected to attend clinic visits every 4 weeks through the End of Treatment visit, according to the study visit schedule, unless consent is actively withdrawn. Complete details are provided in the Time and Events Table (Section 7.1).

If a subject is unable or unwilling to continue attending clinic visits in person, other subject follow-up options to collect subject information as detailed in the informed consent (e.g., telephone calls, letters, review of subjects medical records) should be pursued.

5.5.2. Subjects Who Fail to Attend Clinic Visits

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must 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.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.5.3. Withdrawal from Study

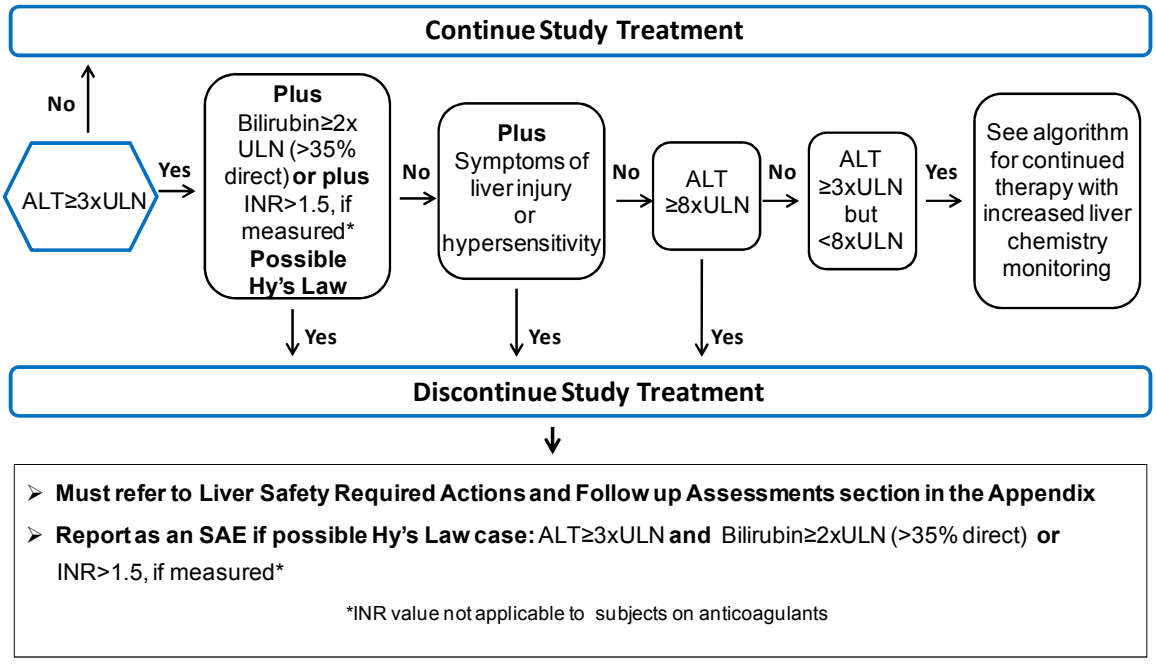
Every effort should be made to keep subjects in the study. For subjects that choose to withdraw consent or are lost to follow up, the reason for not completing the study will be recorded in the subject's eCRF. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Subjects who are withdrawn or discontinue active participation in the study will no longer receive the randomized study treatment. Immediately upon discontinuation from active participation in this study, these subjects should complete the assessments as per the end of treatment clinic visit and return for the post-treatment follow-up clinic visit 8 weeks later (Section 7.1). If a subject is unable or unwilling to return for the follow-up assessments, every effort will be made to follow-up with the subject.

Withdrawn subjects will not be replaced.

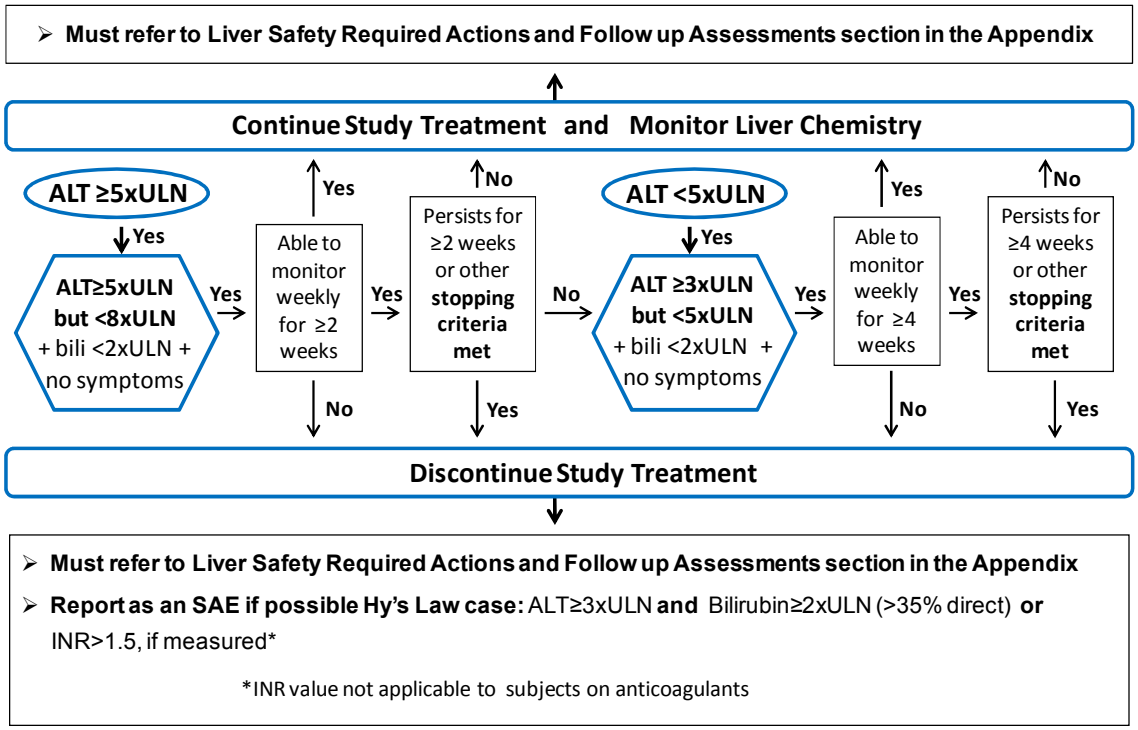
5.5.4. Liver Chemistry Stopping Criteria

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



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

Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



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

5.5.4.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.5.5. QTc Stopping Criteria

- The QT interval corrected for heart rate according to Fridericia's formula (QTcF) *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study.
- The QTcF should be based on a single electrocardiogram (ECGs) obtained over a brief (e.g., 5-10 minute) recording period.
- A subject who meets the following criteria will discontinue investigational product:
  - QTcF >500 msec (or ≥530 msec for subjects with bundle-branch block or pacemaker)

5.6. Subject and Study Completion

A completed subject is one who has completed the 26 week treatment phase of the study. The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment			
Product name:	Lyophilized albiglutide DCC pen injector	Lyophilized albiglutide DCC pen injector matching placebo	Albiglutide liquid auto-injector	Albiglutide liquid auto-injector matching placebo
Dosage form/Delivery system:	Lyophilized albiglutide is provided as a fixed-dose, fully disposable pen injector system for delivery of the study treatment from a prefilled dual chamber glass cartridge (DCC) that is an integral part of the injector pen. It is designed for manual reconstitution of the dose, priming and insertion of the pen needle (29G), and manual injection. The DCC contains lyophilized albiglutide (30mg or 50mg). When the injector pen product is reconstituted a neutral, isotonic solution is produced. The pen delivers albiglutide in an injection volume of 0.5 mL.	Lyophilized albiglutide matching placebo is provided as a fixed-dose, fully disposable pen injector system for delivery of the study treatment from a prefilled DCC that is an integral part of the injector pen. It is designed for manual reconstitution of the dose, priming and insertion of the pen needle (29G), and manual injection. The DCC contains matching placebo. When the injector pen product is reconstituted a neutral, isotonic placebo solution is produced. The pen delivers the placebo in an injection volume of 0.5 mL.	Albiglutide liquid is provided as a fixed-dose, disposable auto-injector containing albiglutide liquid (30 mg or 50 mg) in a prefilled glass syringe with staked 29G thin-wall needle and needle shield. It is intended for single use. The cap remover is removed and the cover sleeve of the auto-injector is pressed against the skin, which results in automatic s.c. injection of the albiglutide liquid. Albiglutide liquid (30mg or 50mg) has a pH of 5.9. The auto-injector delivers the study treatment in an injection volume of 0.6 mL for the 30 mg dose and 1.0 mL for the 50 mg dose.	Liquid albiglutide matching placebo is provided as a fixed-dose, disposable auto-injector containing placebo liquid in a prefilled glass syringe with staked 29G thin-wall needle and needle shield. It is intended for single use. The cap remover is removed and the cover sleeve of the auto-injector is pressed against the skin, which results in automatic s.c. injection of the placebo liquid. The placebo liquid has a pH of 5.9. The auto-injector delivers the placebo in an injection volume of 0.6 mL for the 30 mg placebo dose and 1.0 mL for the 50 mg placebo dose.

	Study Treatment			
Unit dose strength(s) /Dosage level(s):	30mg or 50mg albiglutide	Matching placebo	30mg or 50mg albiglutide	Matching placebo
Route of Administration	Subcutaneous injection in the abdomen, thigh or upper arm region. Rotation of injection sites is recommended.	Subcutaneous injection in the abdomen, thigh or upper arm region. Rotation of injection sites is recommended.	Subcutaneous injection in the abdomen, thigh or upper arm region. Rotation of injection sites is recommended.	Subcutaneous injection in the abdomen, thigh or upper arm region. Rotation of injection sites is recommended.
Dosing instructions:	Administered as a single s.c. injection once a week on the same day each week. Administered by study personnel at the weekly clinic visit. Administered at any time of day without regard to meals.	Administered as a single s.c. injection once a week on the same day each week. Administered by study personnel at the weekly clinic visit. Administered at any time of day without regard to meals	Administered as a single s.c. injection once a week on the same day each week. Administered by study personnel at the weekly clinic visit. Administered at any time of day without regard to meals	Administered as a single s.c. injection once a week on the same day each week. Administered by study personnel at the weekly clinic visit. Administered at any time of day without regard to meals

6.2. Treatment Assignment

Randomized treatment assignment will be done via the Interactive Voice Response System (IVRS), and randomization will be implemented based on a sequestered fixed randomization schedule. Study centre personnel will call the IVRS to execute each randomization once a subject has met all prerequisites for randomization and has completed all scheduled screening assessments.

Subjects will be assigned to study treatment in accordance with the randomization schedule. Eligible subjects will be stratified by age (<65 or ≥65 years of age), weight (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin).

Subjects will be randomized in a 1:1 ratio to either:

- Albiglutide active liquid auto-injector + placebo lyophilized DCC pen injector; or,
- Albiglutide active lyophilized DCC pen injector + placebo liquid auto-injector.

Blinded study centre personnel will receive a randomization notification indicating only the unique subject identifier and the date and time of randomization. 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 study treatment.

6.3. Planned Dose Adjustments

Subjects will receive 30 mg of either albiglutide liquid drug product or albiglutide lyophilized drug product during Weeks 1-4 and will then be up-titrated to 50 mg albiglutide for the remaining 22 weeks of the study (Weeks 5-26).

Down-titration (dose reduction) of albiglutide from 50 mg to 30 mg is **NOT** permitted. If a subject experiences tolerability issues with the higher 50mg dose then the subject may discontinue investigational product (at the discretion of the investigator) and will be followed for safety and efficacy.

The use of metformin in subjects with varying degrees of renal function should be in accordance with the metformin product label. It is encouraged that a stable metformin dose is maintained during the study. However the metformin dose may be downtitrated based on clinical need at the discretion of the investigator. Up-titration of metformin is permitted for subjects who require hyperglycemic rescue and metformin is selected as the rescue medication.

6.4. Blinding

This is a double-blind study; neither the subject nor the study physician will know which of the treatments (albiglutide liquid auto-injector or matching placebo and lyophilized albiglutide DCC pen injector or matching placebo) the subject is receiving. The following will apply.

- 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 Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK 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 eCRF
- If the subject's treatment code is unblinded by the investigator or treating physician the subject will continue to receive treatment unless they meet one of the investigational product discontinuation or study withdrawal criteria outlined in Section 5.5.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required other than that described in Section 6.1.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply and administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).

Further guidance and information for final disposition of unused study treatment are provided in the Study Reference Manual (SRM).

Under normal conditions of handling and administration, study treatment 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. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

The investigator or designee will administer study treatment to the subject in the clinic at the time points specified in the Time and Events Table (Section 7.1). The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.8. 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 subcutaneously every 4 weeks for 12 weeks. This dose was associated with an increased frequency of nausea, vomiting, and headache.

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

6.9. Treatment after the End of the Study

Following completion of the Week 26 visit, eligible subjects who gave consent to participate in the extension study (Study 204682) will be treated as detailed in the extension study protocol. Those subjects who did not give consent to participate in the 26 week extension study will return to the study centre in 8 weeks for the post-treatment follow-up visit (Week 34 visit).

Investigational product will not be provided to subjects by GSK after the end of the study.

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

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

6.10. Concomitant Medications and Non-Drug Therapies

All medications taken at any time from screening to the follow-up visit will be recorded in the eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

6.10.1. Permitted Medications and Non-Drug Therapies

Unless specified as a prohibited medication in Section 6.10.2, all concomitant medications should be considered permitted provided they are not contraindicated in the albiglutide Prescribing Information or for the individual subject concerned. 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.

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

Investigators must adhere to the local labeling of the respective country (e.g., the Summary of Product Characteristics (SmPC) in relevant European countries or the FDA-approved prescribing information) for all permitted medications.

6.10.2. Prohibited Medications and Non-Drug Therapies

Subjects must not use any of the following medications:

- Dipeptidyl peptidase-IV inhibitors and GLP-1R agonists (except albiglutide liquid or lyophilized drug products taken as study treatment) are prohibited.
- Antidiabetic medications other than metformin and study treatment (per study design) unless subjects require antidiabetic medication for hyperglycemic rescue. The preferred post-rescue add-on treatment is insulin. Other medications may be added at the investigator's discretion. The addition of other GLP-1 analogues (i.e., exenatide, or liraglutide, lixisenatide, dulaglutide) is prohibited as the safety of dosing with multiple GLP 1 analogues is unknown. The use of dipeptidyl peptidase-IV inhibitors is prohibited. The addition of a thiazolidinedione (rosiglitazone or pioglitazone) is discouraged.
- Any investigational drug other than the study treatment they have been randomly assigned to.

- Oral or systemically injected corticosteroids (inhaled, intra-articular, epidural, and topical corticosteroids are allowed); 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

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

7. STUDY ASSESSMENTS AND PROCEDURES

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

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

Study visits between Baseline (Week 0) and End of treatment (Week 26) will have a visit window of ±3 days and the follow-up visit (Week 34) will have a visit window of ±7 days. If extraordinary events that make it impossible for subjects to complete a visit/dosing within the visit window (e.g., holidays, personal emergencies), the investigator should contact the medical monitor for advice.

If a subject misses a weekly scheduled visit for receiving albiglutide treatments, the albiglutide treatments should be administered as soon as possible within 3 days after the missed dose. Thereafter, subjects can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, the site staff should wait and administer at the subject's next regularly scheduled visit. If a subject misses 2 or more consecutive dosing, the investigator should contact the medical monitor to discuss options for helping assure better adherence. The medical monitor shall make a decision (on a case by case basis) on whether the subject should continue to receive investigation product.

7.1. Time and Events

Table 4 Schedule of Assessments

Procedure		Treatment													
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
	Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
	Visit Window	-14d	0d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Informed consent		X													
Demography/medical history		X													
HIV, hepatitis B and C, amylase, lipase, alcohol and drug screen, TSH		X													
Inclusion/exclusion criteria review		X	X[1]												
Full (F) or brief (B) physical exam[2]		F	B				B				B				
Height (H),Weigh (W), BMI		H, W, BMI					W				W				
12-lead ECG[3]		X	X		X		X				X				
Vital signs[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum (S)/Urine (U) pregnancy test (WCBP)		S	U	U			U				U				
Clinical chemistry/hematology samples[4]		X		X			X				X				
Lipids (including total cholesterol, LDL-C, HDL C, triglycerides, FFAs)[4]		X													
Urinalysis[5]		X													
HbA_{1c} [6,9]		X	X	X			X				X				X
eGFR		X		X							X				
Immunogenicity sample[7]			X		X		X				X				X
Genetic sample[8]			X												
FPG [9]			X	X	X	X	X	X	X	X	X	X	X	X	X
PK samples[10]															X
Review AE/SAE, concomitant medication and hypoglycemia events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Advice on diet and exercise[11]			X	X	X	X	X	X	X	X	X	X	X	X	X
Register visit into IVRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[12]			X												
Study Treatment			X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4 Schedule of Assessments

Procedure		Treatment													End of Treatment[12,13]	Follow-up[14]
	Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
	Week[15]	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**34**
	Visit Window	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±7d
Informed consent																
Demography/medical history																
HIV, hepatitis B and C, amylase, lipase, alcohol and drug screen, TSH																
Inclusion/exclusion criteria review																
Full (F) or brief (B) physical exam[2]	B			B				B					B	F	F	
Height (H),Weigh (W), BMI	W			W				W					W	W	W	
12-lead ECG[3]														X		
Vital signs		X		X		X		X		X			X	X	X	
Serum (S)/Urine (U) pregnancy test (WCBP)	U			U				U					U	S	U	
Clinical chemistry/hematology samples[4]				X										X		
Lipids (including total cholesterol, LDL-C, HDL C, triglycerides, FFAs)[4]														X	X	
Urinalysis														X		
HbA_{1c} [5,8]				X				X						X	X	
eGFR				X										X	X	
Immunogenicity sample[6]				X				X				X		X	X	
Genetic sample[7]																
FPG [8]	X			X				X						X	X	
PK samples[9]														X		
Review AE/SAE, concomitant medication and hypoglycemia events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Advice on diet and exercise[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Register visit into IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization[11]																
Study Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X			

TSH: thyroid stimulating hormone; BMI: body mass index; WCBP: women of child bearing potential; FFA: free fatty acids; LDL-c: low density lipoproteins cholesterol; HDL-c: high density lipoproteins cholesterol; d, day

1. **Before dosing**, the investigator must review **all** inclusion and exclusion criteria to confirm subject's eligibility. If a subject no longer meets all of the eligibility criteria (e.g., there is evidence of a new myocardial infarction (MI) on an ECG or ALT, etc. are out of range), **do not administer the study treatment** and contact the medical monitor to discuss how to proceed (e.g., to determine if repeat testing is warranted).
2. Details of full and brief physical examinations are provided in Section 7.4.3.
3. 12-lead ECGs will be obtained **before** measurement of vital signs and collection of blood samples for laboratory testing. Vital signs measurement will be taken before collection of blood samples. See Section 7.4.5.
4. Clinical chemistry and hematology assessments are described in Section 7.4.6.
5. Blood samples for HbA_{1c} should be collected before administration of study treatment.
6. Blood samples for immunogenicity are to be collected **before** study drug administration at the times specified in Section 7.1. A follow-up sample will be taken from each subject 8 weeks after the final dose of albiglutide is administered.
7. Blood sample for genetics can be collected at any time during the study after the genetics informed consent has been obtained and the subject has been randomly assigned to treatment group.
8. Subjects will have their FPG and HbA_{1c} levels evaluated to monitor for potential hyperglycemia.
9. PK samples (trough) will be obtained prior to dosing (Section 7.6).
10. Standard diabetic dietary and exercise advice will be provided at Visit 2 and reinforced through the end-of-treatment visit.
11. Once the HbA_{1c} results have been received from the central laboratory and all other eligibility criteria are met, study centre personnel will call the IVRS to obtain the subject's treatment assignment.
12. Subjects who discontinue study treatment should be handled as described in Section 5.5.
13. The end of treatment visit in Study 200952.is also Visit 1 of 204682 for those subjects continuing into the extension study.
14. Follow-up visit for those subjects who have stopped investigational product (see Section 5.5), withdrawn from the study, or who have completed the 26 week treatment period, but do not consent and/or are not eligible to participate in the 26 week extension study (Study 204682).
15. All visits will have a treatment window as in the table. Baseline (Week 0) serves as the reference point. Subjects will not be considered out of compliance if visit windows extend because of extraordinary events that make it impossible for subjects to complete a visit within the above window (e.g., holidays, vacations, personal emergencies). Determination of the maximum visit window deviation is at the discretion of the medical monitor

Table 5 Schedule of Assessments for Subjects Who Permanently Discontinue Investigational Product

Procedure	Continue Scheduled Clinic Visit (Weeks 4, 8, 12, 16, 20) [4, 5]	Week 26 (Equivalent to End of Treatment Visit)	Follow-up Week 34
Full (F) or brief (B) physical exam	B	F	F
Weight	X	X	X
12-lead ECG [1]		X	X
Vital Signs	X	X	X
Clinical chemistry/hematology samples [2]	X	X	X
HbA1c and FPG [3]	X	X	X
Review AE/SAE, concomitant medication and hypoglycemia events	X	X	X

1. 12-lead ECGs will be obtained **before** measurement of vital signs and collection of blood samples for laboratory testing. Vital signs measurement will be taken before collection of blood samples. See Section 7.4.5.
2. Clinical chemistry and hematology assessments are described in Section 7.4.6.
3. Subjects will have their FPG and HbA_{1c} levels evaluated to monitor for potential hyperglycemia.
4. Week will be dependent on when the subject discontinues investigational product. Subjects will start this schedule as soon as possible following investigational product discontinuation and timings of visits will be the same as for if the subject was continuing on investigational product. The timing of the clinic visits can be modified at the discretion of the investigator. All subjects must attend the Week 26 visit.
5. Additional unscheduled visits will occur as medically necessary.

7.2. Screening and Critical Baseline Assessments

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

Demography and medical history (including cardiovascular medical history/risk factors, T2DM history, history of other prior and concomitant medical conditions, and substance usage) will be assessed at screening (as detailed in the eCRF).

Critical baseline assessments will include: HbA_{1c}, FPG and immunogenicity.

Full details of screening and baseline assessments are provided in the Time and Events Table Section 7.1.

7.3. Efficacy

HbA_{1c} and FPG will be measured at the time points specified in the Time and Events Schedule in Section 7.1. Blood samples for HbA_{1c} and FPG should be collected before administration of study treatment.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Unscheduled visits will occur as medically necessary. Detailed procedures for obtaining each assessment are provided in the SRM.

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

The definitions of an AE or SAE can be found in Appendix 5.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.1.1. Time period and Frequency for collecting AE and SAE information

AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).

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

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

All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.

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

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

7.4.1.2. Method of Detecting AEs and SAEs

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

"How are you feeling?"

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

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

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 4.6.1 and Section 7.4.1.5) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5). Further information on follow-up procedures is given in Appendix 5.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRF pages are presented as queries in response to reporting of certain CV (MedDRA) Medical Dictionary for Regulatory Activities terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF page is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

7.4.1.5. AEs of Special Interest

In the Phase IIIa clinical development program, AEs of special interest included several areas of safety related concern for the T2DM population, particularly for a GLP-1R agonist such as albiglutide.

Specific eCRF pages will be used to capture additional details for the following AEs of special interest:

- Hypoglycemic events
- Liver events
- CV events (see Section 7.4.1.4)
- Injection site reactions
- Potential systemic allergic reactions
- Pancreatitis
- MTC
- Diabetic retinopathy
- Pneumonia
- Atrial fibrillation/atrial flutter

The following additional AEs of special interest will be captured in the AE eCRF pages:

- GI events
- Pancreatic cancer
- Malignant neoplasms
- Appendicitis

Subjects with drug hypersensitivity reactions that are not reasonably attributable to another cause or pancreatitis should discontinue investigational product and should not be rechallenged with albiglutide (see Section 5.5 for complete list of AEs of special interest requiring withdrawal).

7.4.1.6. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.4.2. Pregnancy

- If a subject becomes pregnant during the study they should discontinue Investigational Product.
- Any pregnancy that occurs during study participation (i.e., from baseline/randomization through the end of the post-treatment follow-up period) must be reported using a clinical trial pregnancy form.

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

7.4.3. Physical Exams

A full or brief physical examination will be performed at the time points specified in the Time and Events Table Section 7.1

- A full physical examination will include, at a minimum, assessment of the skin (including injection site), head, eyes, ears, nose, throat, thyroid, respiratory system cardiovascular system, abdomen (liver and spleen), lymph nodes, central nervous system and extremities.
- Brief physical examination includes evaluation of skin (including injection site), respiratory system, cardiovascular system, abdomen (liver, spleen), and central nervous system
- Investigators should pay special attention to clinical signs related to previous serious illnesses
- Height will be measured and recorded at screening only. Height should be measured with the subject in indoor daytime clothing with no shoes.

Weight will be measured at the time points specified in the Time and Events Table Section 7.1

Body mass index will be calculated at screening only.

7.4.4. Vital Signs

For vital signs (blood pressure and pulse rate), a single measurement will be taken at each clinic visit (Section 7.1). During visits when ECGs are scheduled, vital sign measurements will be taken after the completion of the ECG sampling. Subjects may be either in a semi-recumbent or seated position. During visits when ECGs are not scheduled, vital sign measurements will be taken while subjects are in a seated position after at least a 5-minute rest period. During visits where a blood draw is required, vital sign measurements will be taken prior to sample collection.

7.4.5. Electrocardiogram (ECG)

- A single 12-lead ECG recording (with subject in semirecumbent position for 10 to 15 minutes before obtaining the ECG) will be performed at the time points specified in the Time and Events Table (Section 7.1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.5.5 for QTc withdrawal criteria.

All ECGs will be performed **before** measurement of vital signs and collection of blood samples for laboratory testing.

Investigators must compare the baseline ECG with the Visit 1 (screening) ECG. Any changes indicative of a new MI or unstable cardiovascular condition (i.e., life-threatening arrhythmia) should prompt the investigator to **not administer the investigational product** but rather to evaluate and treat the subject per local standard of care. If subsequent evaluation reveals that a new MI has occurred or unstable/accelerated angina is documented, then the subject will not be included in the study. If subsequent evaluation reveals no evidence of ischemic damage or instability, then study treatment may proceed. If any screening ECG demonstrates a possible old MI that was unknown to the investigator and the subject, the subject should be evaluated and treated, as appropriate.

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 6 must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule in Section 7.1. Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.

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

All study-required laboratory assessments will be performed by a central laboratory, apart from HbA_{1c} at screening where a local or central laboratory may be used. HbA_{1c} results from a local laboratory must be entered into the eCRF.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 6.

Table 6 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet Count; *Red blood cell (RBC) Indices*: mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH); *White blood cell (WBC) count with Differential:* Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils; RBC Count; Hemoglobin; Hematocrit
Clinical Chemistry [1]	Blood urea nitrogen (BUN); Creatinine; Calcium; bicarbonate; Potassium; Sodium; chloride; Uric acid; Aspartate amino transferase (AST (SGOT)); ALT (SGPT); Alkaline phosphatise; Gamma glutamyl transferase (GGT); Total and direct bilirubin; Total Protein; Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Laboratory Tests	• HbA_{1c} • FPG • Amylase[2,5] • Lipase[2,5] • HIV[2] • TSH[2,3] • Lipids including total cholesterol, LDL-C, HDL C, triglycerides, FFAs (fasting) [4] • Hepatitis B (HBsAg) [2] • Hepatitis C (Hep C antibody) [2] • FSH and estradiol (as needed in women of non-child bearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)[2] • Serum or urine hCG Pregnancy test (as needed for women of child bearing potential)

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.5.4 and Appendix 3.
2. Measured at screening only.
3. Free T4 (reflex) will be measured if TSH is above the upper limit of normal
4. Fasting is defined as no food or drink (except water) for at least 8 hours before blood draw
5. Samples will be stored for calcitonin measurement in the event of MTC related events.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 25 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4.7. Estimated Glomerular Filtration Rate (eGFR)

Serum creatinine will be measured at the time points specified in Time and Events Schedule in Section 7.1. It will be used to calculate eGFR using the MDRD formula [Levey, 2009], namely:

eGFR (ml/min/1.73m2) = 175 x (serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American).

7.4.8. Diabetic Dietary, Exercise, and Home Plasma Glucose Monitoring Advice

Standard diabetic dietary, exercise, and home blood glucose monitoring advice as well as on the signs and symptoms of hypoglycemia and on supplemental oral glucose treatment will be provided at Visit 2 (Week 0) and reinforced at each study site visit through the End of Treatment Visit (Week 26). Subjects should monitor the blood glucose as per the instructions of the investigator and as appropriate for their medical management. The subjects should report promptly, as directed by the investigator, the occurrence of hyperglycemia or hypoglycemia (particularly if symptomatic) to the investigator (or his or her designee). Assessment and action should then occur as deemed appropriate by the investigator.

7.4.9. Hypoglycemic Events

Specific criteria for monitoring hypoglycemic events have been designed to ensure subject safety and to closely monitor hypoglycemia. Hypoglycemic events are defined as follows [Seaquist, 2013]:

Severe Hypoglycemia

- Severe hypoglycemia 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 Hypoglycemia

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

Asymptomatic Hypoglycemia

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

Probable Symptomatic Hypoglycemia

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

Pseudohypoglycemia

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

Any hypoglycemic event, regardless of intensity, that satisfies the definition of an SAE (Appendix 5) should be categorized as outlined in this section and reported appropriately in the SAE eCRF page and the hypoglycemic events AE of special interest page.

7.5. Tracking of Albiglutide Lyophilized DCC Pen Injector and Liquid Auto-injector Failures and User Errors

All albiglutide lyophilized product DCC pen injector and liquid product auto-injector failures and user errors must be detected, documented, and reported by the investigator throughout the study. Detailed information on DCC pen injector and auto-injector failures and user errors will be collected on the Injector Pen and Auto-injector Failure Reporting Form.

NOTE: Albiglutide lyophilized DCC pen injector and liquid auto-injector failures and user errors associated with or resulting in events fulfilling the definition of an AE or SAE will follow the processes outlined in Section 7.4.1.

7.6. Pharmacokinetics

7.6.1. Blood Sample Collection

Blood samples for the determination of albiglutide plasma concentrations will be obtained from all subjects before administration of study treatment according to the Time and Events Table in Section 7.1.During visits where ECGs and vital sign measurements are required, blood samples will be collected **afte**r measurement of ECGs and vital signs.

Blood samples will be collected and stored as detailed in the Laboratory Manual.

7.6.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK, GlaxoSmithKline, the details of which will be included in the Study Reference Manual (SRM). 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 SRM).

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

7.7. Immunogenicity

Serum for antidrug antibody testing will be obtained from all subjects before administration of study treatment at week 0, 2, 4, 8, 12, 16, 20, 24, 26 and at follow-up(wk 34, if applicable),according to the Time and Events Table in Section 7.1

The presence of anti-albiglutide antibodies will be assessed using a validated 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 neutralizing activity. Samples positive for both anti-GLP-1 antibodies and drug neutralizing antibodies may be tested for GLP-1 neutralizing activity (Appendix 7).

Additionally, in the case of severe allergic reactions that include anaphylaxis, angioedema, or other severe potential hypersensitivity reactions, three 1-mL serum samples should be obtained for immunogenicity testing (within 24 hours of the event if possible) and sent to the central laboratory (see details in the SRM) for immediate distribution to a contracted testing facility for specific immunological testing (albiglutide-specific IgE and other tests, as appropriate) A follow-up serum sample will be collected 8 weeks after the final dose of study treatment in the case of early withdrawal from the study.

For subjects who have discontinued study treatment or subjects who have completed the 26 week treatment period, but do not consent and/or are not eligible to participate in the 26 week extension study (Study 204682), if baseline antibody levels or a reduction in titer are not achieved by the follow-up visit then additional samples for immunogenicity testing may be obtained every 30 days following the follow-up visit until baseline antibody levels, or reduced titres, are achieved. Subjects eligible for the extension study (Study 204682) will have immunogenicity samples taken as specified in protocol 204682.

7.8. Genetics

Information regarding genetic research is included in Appendix 4.

8. DATA MANAGEMENT

For this study, subject data will be entered via an eCRF into Oracle Clinical Remote Data Capture (OC RDC) system. Subject data will be available for viewing through access to the OC RDC system. Data provided from other sources will be received, reconciled, combined and transferred to GSK at predetermined time points.

Management of clinical data will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity and quality of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and a validated medication dictionary GSKDrug.

The eCRFs (including queries and audit trails) will be sent at the end of the study in CD format to GSK to be retained. Each investigator will receive a copy of their site specific data in the same format to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary hypothesis is to test that liquid drug product will provide glycemic control (as measured by HbA1c change from baseline) non-inferior to lyophilized drug product for a period of 26 weeks of treatment in subjects with T2DM.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

This study will randomly assign approximately 150 subjects to each of the 2 treatment groups (liquid drug product and lyophilized drug product) in a 1:1 ratio, for a total of approximately 300 subjects. Eligible subjects will be stratified by age (<65 or ≥65 years of age), weight (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin).

With 133 subjects in each of the 2 treatment groups, the study will provide 90% power to demonstrate non-inferiority for HbA1c change from baseline, assuming a non-inferiority margin of 0.4%, an expected treatment group difference of 0.0%, and a common standard deviation of 1%, using a 2-sample, 1-sided t test with significance level of 0.025. Power was calculated using PASS [Hintze, 2013]. Assuming that 13% of subjects will be withdrawn early or will be lost to follow-up; therefore, approximately 150 subjects will be randomized in each treatment group.

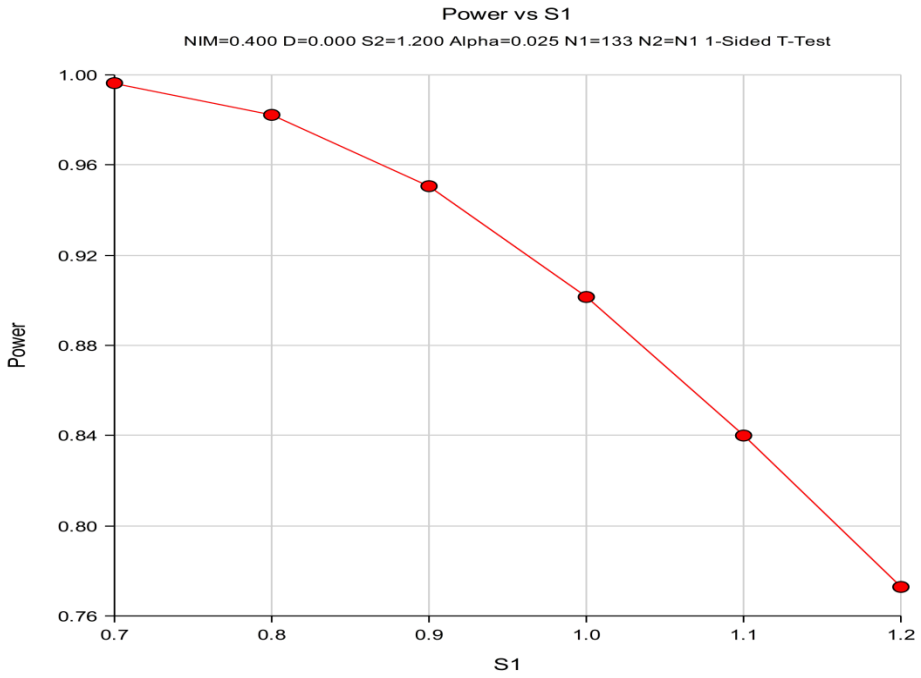
The non-inferiority margin of 0.40 was selected based on the expected effect of the albiglutide lyophilized drug product as active control. Results from two HARMONY

Phase III studies (subset of GLP112756 and GLP112753) for the comparison of the control albiglutide lyophilized drug product versus placebo were used in selecting the non-inferiority margin. The two studies are similar to the current study in terms of the population and the design; subjects were either on diet and exercise or metformin background therapy and received 30 mg of albiglutide then up-titrated to 50 mg albiglutide. The 95% confidence interval from the 2 Harmony studies for HbA1c change from baseline at week 24 for albiglutide lyophilized drug product difference from placebo is (-1.04, -0.75). The conservative effect in terms of the difference from placebo for HbA1c change from baseline at Week 24 for albiglutide lyophilized drug product versus placebo is 0.75% (M1 =0.75%, as defined in Guidance for Industry: Non-Inferiority Clinical Trials [FDA, 2010]). M2, calculated as 50% of M1 is 0.375 (approximately 0.4). The margin of 0.40% that should be met in this trial will preserve at least 45% of the effect of the comparator and it is below M1.

9.2.2. Sample Size Sensitivity

Figure 2 illustrates the power versus standard deviation of 0.7, 0.8, 0.9, 1.0, 1.1, and 1.2 to reject the null hypothesis of inferiority for HbA1c change from baseline, assuming a non-inferiority margin of 0.4%, an expected treatment group difference of 0.0%, and a sample size of 133 per treatment group, using a 2-sample, 1-sided t- test with a significance level of 0.025.

Figure 2 Power of non-inferiority testing for HbA_{1c} different values of Standard Deviations (S1) of 0.7, 0.8, 0.9, 1.0, 1.1, and 1.2



9.2.3. Sample Size Re-estimation or Adjustment

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

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Intent-to-Treat (ITT) Population: The ITT Population will include all randomized subjects who receive at least 1 dose of the study medication and have a baseline assessment. The ITT population will be analyzed according to the randomly assigned treatment. The ITT Population is the primary population for all efficacy analyses.

Safety Population: The Safety Population is defined as all enrolled subjects who receive at least 1 dose of study medication. The subjects in the Safety Population will be analyzed according to the treatment received. The Safety Population will be used for all safety analyses.

Per-Protocol (PP) Population: The PP Population will include all subjects randomly assigned to treatment who complete study procedures through Week 26 and are compliant with the protocol. The subjects in the PP Population will be analyzed according to randomized treatment. The PP Populations may be used for supportive analyses of the efficacy endpoints.

Other analysis populations will be defined in the reporting and analysis plan (RAP).

9.3.2. Interim Analysis

No interim analysis is planned for this study.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

The primary endpoint is the change from baseline in HbA1c at Week 26. The primary analysis will include all HbA1c values collected at scheduled visits up to Week 26. This will include values after hyperglycemia rescue and discontinuation from investigational product. The primary analysis of the primary endpoint will be conducted using a mixed-effect model with repeated measures (MMRM) in the ITT Population. MMRM will use all available data. Imputation under the non-inferiority null hypothesis for missing data will be incorporated [Koch, 2008]. Multiple imputation will be used to replace missing data of change from baseline of HbA1c at Week 26 for all patients in both treatment arms as a first step, and then to make all the imputed values for the liquid drug product arm worse by the non-inferiority margin 0.4.

Multiple imputation approach uses separate covariance parameter estimation for each arm, and also separate regression parameters are estimated on baseline covariates within each arm. For subjects with missing data the imputation will use means and variances-covariances from subjects in that treatment group where that subject with missing data belongs. This approach will be used for all data missing post withdrawal due to lost to follow-up or withdraws consent.

Non-inferiority testing will be performed at a one-sided alpha of 0.025 and non-inferiority margin of 0.4.

Further details of the imputation method for the primary analysis will be provided in the RAP.

The primary MMRM model will include HbA1c change from baseline at all post-baseline visits as dependent variables; treatment, region, age category, weight, background antidiabetic therapy, visit week, and treatment-by-week interaction as fixed effects; baseline HbA1c as a continuous covariate; and subject as a random effect. Treatment effects estimates (and associated CI) of albiglutide liquid drug product will be evaluated within this MMRM model as least squares means contrasts relative to the lyophilized drug product. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion.

9.4.2. Secondary Analyses

The evaluation of the safety and tolerability as assessed by immunogenicity and ISRs of albiglutide liquid drug product and the lyophilized drug product will be provided by reporting the event rates, and the associated 95% CI.

The overall general safety and tolerability of albiglutide liquid drug product versus lyophilized drug product will be evaluated in tabular and/or graphical format and summarized descriptively.

AEs and SAEs, physical examinations, clinical laboratory evaluations, vital sign measurements, and 12-lead electrocardiogram will be summarized by treatment group. For continuous variables, these summaries will include sample size, mean, median, standard deviation (and/or standard error), minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. The exposure-adjusted incidence rate will also be calculated as the number of events in a given period divided by the total person time on treatment of subjects at risk within the same period. The exposure-adjusted incidence rate will be expressed as an annualized rate expected. No inferential testing will be performed on the safety variables. Hypoglycemic events will be analyzed separately from other AEs. All hypoglycemic events will be classified as severe, documented symptomatic, asymptomatic, probable symptomatic, and pseudohypoglycemia, as defined in Section 7.4.9.

AEs will be coded using MedDRA. AEs will be summarized in various subsets, including on therapy AEs, related AEs, AEs leading to treatment discontinuation or withdrawal from study, SAEs, fatal AEs, etc. AEs will also be summarized by maximum intensity (mild, moderate, and severe).

Anti-albiglutide antibody results will be summarized by treatment group. In addition, the number and percentage of subjects with positive results along with the antibody titer values will be provided by visit.

The secondary endpoint FPG change from baseline at Week 26 will be analyzed using MMRM without imputation.

To assess the PD effect of albiglutide over time for the secondary endpoints change from baseline in HbA1c over time and change from baseline in FPG over time MMRM models will be used. The model will include HbA1c or FPG change from baseline at all post-baseline visits as dependent variables; treatment, visit week, and treatment-by-week interaction as fixed effects; baseline HbA1c or FPG as a continuous covariate; and subject as a random effect. Treatment effects estimates (and associated CI) of albiglutide liquid drug product will be evaluated within this MMRM model as least squares means contrasts relative to the lyophilized drug product. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion. In addition, PD effect of albiglutide over time for both HbA1c and FPG change from baseline over time will be evaluated in tabular and/or graphical format and summarized descriptively.

PK trough plasma concentration data will be summarized by treatment. No formal statistical analyses will be conducted.

9.4.3. Other Analyses

The analyses of the primary and secondary efficacy endpoints are described in Section 9.4.1 and Section 9.4.2. The details of any further planned analyses, including subgroup analysis and exploratory endpoints, will be provided in the RAP.

9.4.4. Supportive Analyses for Primary Endpoint

The primary endpoint change from baseline in HbA1c at Week 26 will be analyzed using the same MMRM model as described in Section 9.4.1 but missing data are not explicitly imputed in this supportive analysis; although, there is an underlying assumption that data is missing at random. All available scheduled post-baseline assessments up to endpoint are utilized and, via modeling of the within subject correlation structure, the derived treatment difference at Week 26 is adjusted to take into account missing data. The MMRM analysis (using saturated fixed effects and an unstructured variance-covariance matrix) is considered appropriate as the supportive analyses, as it has been shown to give sensible answers to on-treatment questions in a range of practical situations [Siddiqui, 2009].

Analysis excluding post-rescue and/or discontinuation from investigational product HbA1c data will also be performed as supportive. It is not expected to have a substantial number of subjects who will require rescue and that number of subjects would be similar for both treatment arms. However, to assess the impact of rescue, analysis of pre-rescue data will be performed. The MMRM model will be similar to the one used for the primary analysis. Results of this analysis will supplement the primary analysis. No imputation will be conducted for this supportive analysis.

The primary endpoint HbA1c change from baseline at Week 26 may also be analyzed using MMRM model in the PP Population, if sample size is sufficient, imputation will not be conducted for this supportive analysis.

Further details of the supportive analyses will be provided in the RAP.

9.4.5. Missing Data

9.4.5.1. Impact of Missing Data on Primary Endpoint

Missing data, in the context of the primary analysis at Week 26, refer to those cases where the Week 26 HbA1c value is not available or was not collected or subject is lost to follow-up or withdraws consent. Missing data will be imputed in the primary MMRM analysis. To avoid bias in non-inferiority trials due to missing data, special attention will be paid to the handling of missing data in statistical analysis. Although, it is expected that the pattern of missing data will be similar in both treatment arms given that the treatment arms are the same drug but different formulations and it is expected that the impact of missing data on the primary endpoint to be minimal. Imputation under the non-inferiority null hypothesis [Koch, 2008] for all missing data for the primary analysis at Week 26 will be implemented.

9.4.5.2. Extent of Missing Primary Analysis Data

Missing data is expected to arise mainly from subjects missing complete visits. The amount of missing data for those baseline covariates included in the statistical analysis is expected to be none or at worst minimal. If it should occur, that subject will effectively be lost to analysis. Missing data for HbA1c between two non-missing visits will be considered missing at random (intermediate missing data).

In this study, subjects who withdraw from treatment will stay in the study. In the eCRF, the reason for treatment discontinuation and the reason for withdrawal from the study are collected separately. Whenever the HbA1c value at Week 26 is missing (end of the study), the reason can be determined based on available data in these two locations.

The reason for missing data can be classified as lost to follow-up or withdrawal of consent.

9.4.5.3. Reasons for Withdrawal

Reasons for withdrawal from the study are lost to follow-up or withdrawal consent. All subjects who discontinuation from investigational product due to the reasons listed under Section 5.5 will remain in the study and efficacy and safety data will be collected.

9.4.5.4. Handling of Missing Data

The impact of missing data will be explored, as outlined below, for the ITT Analysis Population only.

Examination of Missing Data Patterns

It is expected that the pattern of missing data will be similar in both treatment arms given that each treatment arm is using the same drug but different formula.

To examine the nature of missing data, due to lost to follow-up or withdrawal consent, cohorts of subjects will be defined based on the scheduled assessments (HbA1c change from baseline) that were completed at Weeks 1, 4, 8, 12, 16, 20, and 26.

- Subjects who have week 1 assessment only
- Subjects who have assessments up to and including Week 4 only
- Subjects who have assessments up to and including Week 8 only
- Subjects who have assessments up to and including Week 12 only
- Subjects who have assessments up to and including Week 16 only
- Subjects who have assessments up to and including Week 20 only
- Subjects who have assessments up to and including Week 26.

The number and percentage of subjects on each treatment in the 7 cohorts defined here will be tabulated. Graphical methods will be used to examine changes from baseline over time to assess the pattern of outcomes prior to withdrawal.

Sensitivity Analyses

The sensitivity of the results of analysis to the method of handling missing values will be investigated, especially if the number of missing values is substantial or if the characteristics of missing values differ between treatment groups.

To assess the impact of subjects who discontinued investigational product and stayed in the study; exclusion of data after treatment discontinuation may also be performed if a significant number of subjects discontinue study medication prior to Week 26. On treatment data will be analyzed using MMRM model as described in Section 9.4.1. Week 26 observations off-treatment will be imputed under the non-inferiority null hypothesis [Koch, 2008].

Sensitivity analyses using a different type of multiple imputation method will be conducted. Firstly, missing data between two non-missing time points will be considered missing at random (MAR). The analyses using the last mean carried forward (LMCF) approach will be performed using the following rates of HbA1c increase: 0%/month, 0.1%/month, and 0.2%/month to explore the potential impact as in a tipping-point analysis. For each treatment group, these 3 rates will be assumed, resulting in 9 scenarios. The resulting treatment differences and associated P-values for non-inferiority will be tabulated against the varying rates of HbA1c increase. This estimand is one where those who withdraw are assumed to revert to an unstable treatment regimen with an increasing rate of HbA1c. For each imputation data set, an analysis of variance will be carried using Week 26 data, both actual and imputed, using the same covariates as in the primary

analysis. Contrasts of interest will be estimated and then combined across imputations using standard multiple imputation rules.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study (and for amendments as applicable).
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

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

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

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the

investigator or the head of the medical institution, where applicable, of the impending action.

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

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at 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 randomization codes for their site only after completion of the full statistical analysis.

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

10.8. Review Committees

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

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPK	creatine phosphokinase
CV	cardiovascular
DCC	dual chamber cartridge
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FFA	free fatty acids
FPG	fasting plasma glucose
FRP	females of reproductive potential
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GSK	GlaxoSmithKline
HA	human albumin
HbA1c	glycated hemoglobin
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
hCG	human chorionic gonadotrophin
HDL-c	high density lipoproteins
HRP	horseradish peroxidase
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonization

IEC	Independent Ethics Committee
INR	international normal range
IP	investigational product
IRB	Institutional Review Board
ISRs	injection site reactions
ITT	intent-to-treat
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LDL-c	low density lipoproteins;
LMCF	last mean carried forward
K_2EDTA	di-potassium ethylenediaminetetraacetic acid
MACE	major adverse cardiovascular event
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MI	myocardial infarction
MMRM	mixed-effect model with repeated measures
MNAR	missing not at random
MSDS	Material Safety Data Sheet
MTC	medullary thyroid cancer
OC RDC	Oracle Clinical Remote Data Capture
PAC	Pancreatitis Adjudication Committee
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
PTS-DPMK	Platform Technologies and Science-Drug Metabolism and Pharmacokinetics
RAP	Reporting Analysis Plan
RBC	red blood cell
RNA	ribonucleic acid
s.c.	subcutaneous
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SRM	Study Reference Manual
SU	sulfonylureas
T2DM	type 2 diabetes mellitus
TSH	thyroid stimulating hormone
ULN	upper limit of normal range
WBC	white blood cell
WCBP	women of child bearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA
SpectraMAX

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

19. Contraceptive subdermal implant that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label.
20. Intrauterine device or intrauterine system that meets effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Trussell, 2011]
21. Oral Contraceptive, either combined or progestogen alone [Trussell, 2011]
22. Injectable progestogen [Trussell, 2011]
23. Contraceptive vaginal ring [Trussell, 2011]
24. Percutaneous contraceptive patches [Trussell, 2011]
25. Male partner sterilization prior to the **female subject's entry** into the study, and this male is the sole partner for that subject. The information on the male sterility can come from interview with the subject on her male partner's medical history.
26. Male condom **combined with a female** diaphragm, with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

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

References

Trussell J, Contraceptive Efficacy. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Kowal D, and Policar M (editors). Contraceptive Technology: Twentieth Revised Edition. New York: Ardent Media, 2011.Table 26-1

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

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria - Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 5xULN but <8xULN persists for ≥2 weeks

ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks

ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment

• Report the event to GSK within 24 hours

• Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]

• Perform liver event follow up assessments

• Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see MONITORING below)</td><td>• Viral hepatitis serology[4]

• 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[5].

• Blood sample for PK analysis, obtained within 3 half-lives (15 days) after last dose[6]

• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</td></tr>
</table>

Liver Chemistry Stopping Criteria - Liver Stopping Event	
• **Do not restart/rechallenge** subject with study treatment • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adducts HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding**

studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants

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

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **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. • Subject can continue study treatment • Subject 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 subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

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

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

12.4. Appendix 4: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- T2DM susceptibility, severity, and progression and related conditions.

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

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

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labeled (or "coded") with the same study specific number used to label other samples and data in the study. This number 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).

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 only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

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

Informed Consent

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

Subject Withdrawal from Study

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

Continue to participate in the genetic research in which case the genetic DNA sample is retained

Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.

Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

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

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

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

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

12.5.1. Definition of Adverse Events

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

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

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's

condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.5.2. Definition of Serious Adverse Events

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

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

a. Results in death

b. Is life-threatening

NOTE:

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

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

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, 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. Other situations:

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

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

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

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

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

12.5.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.5.4. Recording of AEs and SAEs

AEs and SAE Recording:

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

12.5.5. Evaluating AEs and SAEs

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor or the SAE coordinator • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: Collection of Pregnancy Information

Pregnancy information on female study subjects

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to GSK as described in Appendix 5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- Will discontinue study medication.

12.7. Appendix 7: Immunogenicity Testing Algorithm

The immunogenicity of albiglutide will be evaluated using the following testing schemes and assays.

Sample Testing Schemes

Samples for immunogenicity testing will be obtained as detailed in the time and events schedule (Section 7.1) and Section 7.7.

The presence of anti-albiglutide antibodies will be assessed using a validated screening enzyme-linked immunosorbent assay (ELISA). If serum samples contain anti-albiglutide antibodies, they will be further analyzed in a confirmation assay to show specificity for albiglutide. Confirmed positive samples will be titrated to obtain the anti-albiglutide titer value. To test whether anti-albiglutide antibodies cross-react with endogenous glucagon-like peptide (GLP-1) or human albumin (HA), positive samples will be tested in secondary assays which include anti-GLP-1or anti-HA screening ELISA's, respectively. In addition, anti-albiglutide positive samples will be tested for neutralizing activity against the drug in a cell-based assay. Subjects that are positive for anti-albiglutide neutralizing antibodies and anti-GLP-1 antibodies may be assessed in an anti-GLP-1 neutralizing antibody assay for neutralizing activity against GLP-1.

Antibody Detection Assays

The detection assays are ELISA- based and utilize a tiered testing approach. The anti-albiglutide assay includes screening, confirmation and titration assays. The anti-GLP-1 ELISA includes screening and confirmation steps. For the anti-HA ELISA only a screening step is feasible.

The procedure for the albiglutide immunoglobulin (IgG/A/M) ELISA is described below:

1. 96-well ELISA plates are coated with albiglutide overnight.
2. Samples are diluted 1:50 and incubated on blocked plates for 3 hours.
3. A horseradish peroxidase (HRP)-labeled anti-human IgG/A/M antibody is used as the detection antibody.
4. A tetramethylbenzidine peroxidase substrate is used to produce the enzymatic reaction which is followed by an acid stop procedure.
5. The plates are read at 450 nm using a SpectraMax Plus 384 reader (Molecular Devices LLC, Sunnyvale, California), or the equivalent.
6. A positive control (normal human serum pool spiked with anti-human GLP-1 antibody) and negative control (pooled normal human serum) 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 T2DM 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 immobilized 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 neutralizing antibody assay and other secondary assays.

Titration

Confirmed positive samples will be titrated to obtain a titer value of anti-albiglutide antibody.

Neutralizing Antibody Assays

The neutralizing antibody assays are cell-based reporter gene assays, which include screening, confirmation and titration assays. Albiglutide-neutralizing 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 neutralizing activity will generate a reduced signal and will be further tested in confirmation (specificity) assay if the generated signal is positive (i.e., below the assay's screening cutoff). Confirmed positive samples will be titrated to obtain a titer value of neutralizing anti-albiglutide antibody.

Immunogenicity Testing Report

The immunogenicity testing report will include the incidence of immunogenicity, incidence of neutralizing antibodies and the antibody titers (binding and neutralization to albiglutide). Cross-reactive antibodies to GLP-1 and HA will be discussed.

12.8. Appendix 8: Country Specific Requirements

No country-specific requirements exist.

12.9. Appendix 9: Protocol Amendment Changes

Changes Resulting from Protocol Amendment 1

This amendment is applicable to all participating countries.

Summary of Changes

1. Benefit risk table modified to provide further details relating to mitigation strategies.

2. Exclusion criteria related to abnormal TSH modified.

3. Exclusion criteria numbering corrected. Exclusion criteria for 'fasting triglyceride level >750 mg/dL at screening' was un-numbered and formed part of exclusion criteria 14.

4. Exclusion criteria relating to positive urine drug screen result at Screening modified.

5. New text to clarify visit windows.

6. Time and Event Table modified to add HbA1c sample at Week 12

7. Time and Event Table modified to remove the Week 13 PK sample and add a PK sample at Week 12.

8. Details for collection of PK samples moved to SPM.

9. Timings for handling of missing data changed.

List of Specific Changes

Amendment 1:

Section 4.6.1, Table 2, Risk Assessment for Albiglutide

Original text:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Pancreatitis	Acute pancreatitis has been reported in association with albiglutide and other GLP-1 receptor agonists in clinical trials and during postmarketing experience. Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether they are at increased risk for pancreatitis.	Subjects with a history of acute or chronic pancreatitis are excluded from entering the study (See Section 5.2). Subjects will be informed of the characteristic symptom of pancreatitis: persistent severe abdominal pain. If pancreatitis is suspected, albiglutide should be promptly discontinued and if pancreatitis is confirmed, study treatment will not be restarted (see Section 5.5). Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
Gastrointestinal (GI) events.	Albiglutide has not been studied in subjects with severe GI disease, including severe gastroparesis. Use of albiglutide can be associated with GI side effects such as diarrhea, nausea, and vomiting.	Subjects with severe gastroparesis are excluded from entering the study (See Section 5.2). Subjects with a history of significant GI surgery that in the opinion of the investigator is likely to significantly affect upper GI or pancreatic function are excluded from entering the study (See Section 5.2). Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
Hypoglycemia.	Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycemia when used as monotherapy or in combination with agents such as metformin which also have low intrinsic risk for significant	***All subjects are required to have a last indicator of glycemic control of above HbA_{1c} = 7% which is expected to reduce the risk of hypoglycemia when***

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	hypoglycemia.	***starting albiglutide.*** Subjects are neither allowed to use insulin nor insulin secretagogues during the study. Except as part of hyperglycemia rescue (see Section 5.4) Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
Immunogenicity (e.g., including anti-drug antibodies, clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, and other potential immune-related AEs).	***Hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III program with lyophilized albiglutide. In the Phase III program one subject (anti-albiglutide antibody negative) developed rash and itching; and upon rechallenge recurrence of these symptoms associated with dyspnea.*** Risk assessment of the albiglutide molecule predicted low immunogenic potential, which was substantiated for the commercial lyophilized DCC pen injector product in the registration program. Treatment-emergent anti-drug antibodies were detected in ~5% subjects over studies of up to 3 years duration and were generally transient, of low titer, and not neutralizing. Subjects who tested positive for anti-albiglutide antibodies experienced a similar glycemic response (HbA1c and fasting plasma glucose) to those who did not test positive for antibodies. Other than injection site reactions (see below), the overall safety profile appeared similar among the subset of subjects who did and those who did not test positive for anti-albiglutide antibodies. Changes in the propensity of the liquid product to form aggregates could have an impact on anti-drug antibody characteristics or immune related AEs. However, the likelihood of clinically important changes in anti-drug antibody characteristics or immune related AEs with the liquid albiglutide drug product compared to the lyophilized drug product is considered low based on the absence of substantive qualitative differences between formulations.	A pre-exposure baseline serum sample will be taken and tested for pre-existing ADAs. The development of anti-albiglutide antibodies will be assessed as part of this study.
Injection site reactions (ISRs)	Albiglutide injections may cause rash, erythema or itching and/or other reactions at the site of injection. In the Phase III program with the lyophilized drug product, most subjects with	Subjects will be advised that when injecting in the same region, to use a different injection site each week. Risk communication via guidance for investigators (see

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	ISRs did not test positive for anti-albiglutide antibodies. However, injection site reactions were reported more frequently among those who did test positive for anti-albiglutide antibodies (41% of the ADA positive subjects reported one or more injection site reactions) than among those who were consistently antibody negative (14% of the antidrug antibody negative subjects reported one or more injection site reactions). Overall, for albiglutide, injection site reactions have not been associated with clinically significant sequelae; although they can be a tolerability issue and were the most common reason for withdrawal of study medication for subjects (approximately 2.0%) in the albiglutide group. Differences between formulation characteristics (e.g. lower pH and larger volume for the 50 mg dose of the liquid formulation) may impact the injection site reaction profile.	Section 6 of the IB) and informed consent form for subjects.
Other adverse reactions (e.g., pneumonia, atrial fibrillation/atrial flutter, appendicitis, ***and hypersensitivity reactions***)	In the Phase III program in T2DM, other possible albiglutide related adverse reactions were identified. These events occurred at a cumulative incidence <3% in studies up to 3 years in duration. These events were reported more frequently with albiglutide than comparators.	***Subjects with a known allergy to albiglutide or any product components (including yeast and human albumin) are excluded from the study (See Section 5.2).*** Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
Thyroid C-cell tumors	GLP-1 receptor agonists, including albiglutide increase serum calcitonin in rodents and other GLP-1 receptor agonists are associated with thyroid C-cell focal hyperplasia and C-cell tumors in rodents It is unknown whether GLP-1 receptor agonists are associated with thyroid C-cell tumors in humans, including medullary thyroid cancer (MTC).	Subjects with a personal or family history of MTC or subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) are excluded from the study (See Section 5.2). Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. Routine monitoring of serum calcitonin is not recommended. However, if serum calcitonin is found to be elevated the subject should be referred to a specialist for further evaluation. If MTC or other thyroid C-cell neoplasia is diagnosed, study treatment will be discontinued (see Section 5.5).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other malignant neoplasms	Theoretical concerns have been raised regarding use of incretin based therapies and other malignancies such as pancreatic cancer [Egan, 2014] and malignancy when used in combination with insulin based on hypotheses of biological plausibility [European Public Assessment Report, 2014], and hematological malignancies [FDA Summary Basis of Approval, 2014].	Subjects with a history of cancer that has not been in full remission for at least 3 years before screening are excluded from the study (See Section 5.2). ***Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.***
Cardiovascular (CV) safety of antidiabetic therapy	T2DM is associated with an elevated risk of CV disease. Global regulatory agencies require new antidiabetic therapies to demonstrate that the new therapy is not associated with an unacceptable increase in CV risk. In the Phase III registration program, an independent Clinical Endpoint Committee prospectively adjudicated blinded CV events. The final CV meta-analysis showed no increased CV risk (MACE [major adverse cardiovascular event] + composed of CV death, myocardial infarction [MI], stroke, and hospitalization for unstable angina) with albiglutide versus all comparators (MACE+ hazard ratio = 1.00; 95% CI: 0.68, 1.49).	Subjects with clinically significant CV and/or cerebrovascular disease within 3 months before screening will be excluded from the study. Further details are provided in Section 5.2 Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
Hepatotoxicity	Hepatotoxicity is an area of interest in drug development. Patients with T2DM are at increased risk for liver enzyme abnormalities and disease related liver conditions. One subject treated with albiglutide in the Phase III clinical program developed probable drug induced liver injury with an asymptomatic elevation in alanine amino transferase (ALT) and total bilirubin although the cases had some atypical features and complicating factors .	Routine liver safety laboratory evaluations will be conducted and specific withdrawal criteria for elevated liver function tests have been defined (See Section 5.5.1).
Subject population with severe renal impairment (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2)	Experience in T2DM subjects with severe renal impairment is limited (in the Phase III programme a total of 19 subjects with eGFR <30 mL/min/1.73m^2 received albiglutide). In a Phase III study of patients with varying degrees of renal impairment, in the albiglutide group, on-therapy GI AEs occurred with a higher incidence and higher event rate in subjects with moderate and severe renal impairment compared to those with mild renal impairment. GI events may lead to dehydration and worsen renal function.	Subjects with an eGFR ≤30 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease (MDRD) formula) are excluded from the study (see Section 5.2). Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Drug interactions	Albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the development program, drug interactions studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant PK or PD effects.	Investigators will be advised to take the effect of albiglutide on gastric emptying into account when prescribing concomitant medication.
Fetal & neonatal developmental toxicity	Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Albiglutide administration during the major period of organogenesis in female mice resulted in embryofetal lethality, and bent/wavy ribs in the fetus at 50 mg/kg/day. Given that albiglutide is an albumin-based protein therapeutic, it is likely to be transferred to breast milk ***and may increase neonatal β–cell mass.*** Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation.	Subjects who are breastfeeding, pregnant or planning a pregnancy during the course of the study are excluded. Additionally, all females of child-bearing potential must be taking adequate contraception during the study and have a negative pregnancy test prior to entry. See Section 5.1 for further details.
Accelerated sexual maturation in juveniles	Long-acting GLP-1R agonists have the potential to accelerate sexual maturation in monkeys based on absolute testes weight and similar trends in prostate, seminal vesicle, epididymides weights and histological assessment of maturity.	Subjects under 18 years of age are excluded (see Section 5.1).
Albiglutide matching placebo injections	Albiglutide placebo injections using the lyophilized DCC pen injector were associated with a clinically relevant rate of injection site reactions in the Phase III studies. There is no experience with placebo injections using the liquid auto-injector, including volume and pH differences from the lyophilized product placebo.	Subjects will be advised that when injecting in the same region, to use a different injection site each week. ***Risk communication via informed consent form for subjects.***

Amended text:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Pancreatitis	Acute pancreatitis has been reported in association with albiglutide and other GLP-1 receptor agonists in clinical trials and during postmarketing experience. Albiglutide has not been studied in subjects with a history of pancreatitis to	Subjects with a history of acute or chronic pancreatitis are excluded from entering the study (See Section 5.2). Subjects will be informed of the characteristic symptom of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	determine whether they are at increased risk for pancreatitis.	pancreatitis: persistent severe abdominal pain. If pancreatitis is suspected, albiglutide should be promptly discontinued and if pancreatitis is confirmed, study treatment will not be restarted (see Section 5.5). Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
Gastrointestinal (GI) events.	Albiglutide has not been studied in subjects with severe GI disease, including severe gastroparesis. Use of albiglutide can be associated with GI side effects such as diarrhea, nausea, and vomiting.	Subjects with severe gastroparesis are excluded from entering the study (See Section 5.2). Subjects with a history of significant GI surgery that in the opinion of the investigator is likely to significantly affect upper GI or pancreatic function are excluded from entering the study (See Section 5.2). Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
Hypoglycemia.	Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycemia when used as monotherapy or in combination with agents such as metformin which also have low intrinsic risk for significant hypoglycemia.	***To reduce the risk of hypoglycemia when starting albiglutide all subjects are required to have HbA1c ≥7.0 at screening (see Section 5.1).*** Subjects are neither allowed to use insulin nor insulin secretagogues during the study. Except as part of hyperglycemia rescue (see Section 5.4) Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
Immunogenicity (e.g., including anti-drug antibodies, clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, and other potential	Risk assessment of the albiglutide molecule predicted low immunogenic potential, which was substantiated for the commercial lyophilized DCC pen injector product in the registration program. Treatment-emergent anti-drug antibodies were detected in ~5% subjects over studies of up to 3 years duration and were generally transient, of low titer, and not neutralizing.	A pre-exposure baseline serum sample will be taken and tested for pre-existing ADAs. The development of anti-albiglutide antibodies will be assessed as part of this study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
immune-related AEs).	Subjects who tested positive for anti-albiglutide antibodies experienced a similar glycemic response (HbA1c and fasting plasma glucose) to those who did not test positive for antibodies. Other than injection site reactions (see below), the overall safety profile appeared similar among the subset of subjects who did and those who did not test positive for anti-albiglutide antibodies. Changes in the propensity of the liquid product to form aggregates could have an impact on anti-drug antibody characteristics or immune related AEs. However, the likelihood of clinically important changes in anti-drug antibody characteristics or immune related AEs with the liquid albiglutide drug product compared to the lyophilized drug product is considered low based on the absence of substantive qualitative differences between formulations.	
Hypersensitivity Reactions	***Systemic allergic/hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III program with lyophilized albiglutide. Data have not demonstrated an association of albiglutide with an increased incidence of anaphylaxis, angioedema, or urticaria. However, there was one non-serious hypersensitivity event (rash and itching associated with dyspnea upon rechallenge) that was consistent with a possible albiglutide-related systemic hypersensitivity reaction in a female subject who was anti-albiglutide antibody negative. See Section 5.4 of the IB.***	***Subjects with a known allergy to albiglutide or any product components (including yeast and human albumin) are excluded from the study (See Section 5.2).*** ***Subjects will be informed of the symptoms of severe hypersensitivity or allergy and be advised to seek medical assistance immediately.*** ***Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.***
Injection site reactions (ISRs)	Albiglutide injections may cause rash, erythema or itching and/or other reactions at the site of injection. In the Phase III program with the lyophilized drug product, most subjects with ISRs did not test positive for anti-albiglutide antibodies. However, injection site reactions were reported more frequently among those who did test positive for anti-albiglutide antibodies (41% of the ADA positive subjects reported one or more injection site reactions) than among those who were consistently antibody negative (14% of the antidrug antibody negative subjects reported one or more injection site reactions). Overall, for albiglutide, injection site reactions have not been associated with	Subjects will be advised that when injecting in the same region, to use a different injection site each week. Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects. ***The development of injection site reactions will be assessed as part of this study.***

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	clinically significant sequelae; although they can be a tolerability issue and were the most common reason for withdrawal of study medication for subjects (approximately 2.0%) in the albiglutide group. Differences between formulation characteristics (e.g. lower pH and larger volume for the 50 mg dose of the liquid formulation) may impact the injection site reaction profile.	
Other adverse reactions (e.g., pneumonia, atrial fibrillation/atrial flutter, appendicitis)	In the Phase III program in T2DM, other possible albiglutide related adverse reactions were identified. These events occurred at a cumulative incidence <3% in studies up to 3 years in duration. These events were reported more frequently with albiglutide than comparators.	Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
Thyroid C-cell tumors	GLP-1 receptor agonists, including albiglutide increase serum calcitonin in rodents and other GLP-1 receptor agonists are associated with thyroid C-cell focal hyperplasia and C-cell tumors in rodents It is unknown whether GLP-1 receptor agonists are associated with thyroid C-cell tumors in humans, including medullary thyroid cancer (MTC).	Subjects with a personal or family history of MTC or subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) are excluded from the study (See Section 5.2). Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. Routine monitoring of serum calcitonin is not recommended. However, if serum calcitonin is found to be elevated the subject should be referred to a specialist for further evaluation. If MTC or other thyroid C-cell neoplasia is diagnosed, study treatment will be discontinued (see Section 5.5).
Other malignant neoplasms	Theoretical concerns have been raised regarding use of incretin based therapies and other malignancies such as pancreatic cancer [Egan, 2014] and malignancy when used in combination with insulin based on hypotheses of biological plausibility [European Public Assessment Report, 2014], and hematological malignancies [FDA Summary Basis of Approval, 2014].	***Relevant data on pancreatic cancer are summarized in IB Section 5.4.*** Subjects with a history of cancer that has not been in full remission for at least 3 years before screening are excluded from the study (See Section 5.2).
Cardiovascular (CV) safety of antidiabetic therapy	T2DM is associated with an elevated risk of CV disease. Global regulatory agencies require new antidiabetic therapies to demonstrate that the new therapy is not associated with an unacceptable increase in CV risk. In the Phase III registration program, an independent Clinical Endpoint Committee prospectively adjudicated blinded CV events. The final CV meta-	***Relevant data on cardiovascular events are summarized in IB Section 5.4.*** Subjects with clinically significant CV and/or cerebrovascular disease within 3 months before screening will be excluded from the study. Further details are

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	analysis showed no increased CV risk (MACE [major adverse cardiovascular event] + composed of CV death, myocardial infarction [MI], stroke, and hospitalization for unstable angina) with albiglutide versus all comparators (MACE+ hazard ratio = 1.00; 95% CI: 0.68, 1.49). ***See Section 5.4 of the IB.***	provided in Section 5.2 Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
Hepatotoxicity	Hepatotoxicity is an area of interest in drug development. Patients with T2DM are at increased risk for liver enzyme abnormalities and disease related liver conditions. One subject treated with albiglutide in the Phase III clinical program developed probable drug induced liver injury with an asymptomatic elevation in alanine amino transferase (ALT) and total bilirubin although the cases had some atypical features and complicating factors .	Routine liver safety laboratory evaluations will be conducted and specific withdrawal criteria for elevated liver function tests have been defined (See Section 5.5.1).
Subject population with severe renal impairment (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2)	Experience in T2DM subjects with severe renal impairment is limited (in the Phase III programme a total of 19 subjects with eGFR <30 mL/min/1.73m^2 received albiglutide). In a Phase III study of patients with varying degrees of renal impairment, in the albiglutide group, on-therapy GI AEs occurred with a higher incidence and higher event rate in subjects with moderate and severe renal impairment compared to those with mild renal impairment. GI events may lead to dehydration and worsen renal function.	Subjects with an eGFR ≤30 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease (MDRD) formula) are excluded from the study (see Section 5.2). Risk communication via guidance for investigators (see ***Section 5.4 and*** Section 6 of the IB) and informed consent form for subjects.
Drug interactions	Albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the development program, drug interactions studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant PK or PD effects.	Investigators will be advised to take the effect of albiglutide on gastric emptying into account when prescribing concomitant medication.
Fetal & neonatal developmental toxicity	Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Albiglutide administration during the major period of organogenesis in female mice resulted in embryofetal lethality, and bent/wavy ribs in the fetus at 50 mg/kg/day. ***Offspring of mice dosed with 50 mg/kg/day during organogenesis had reduced pre-weaning body weight (which recovered after weaning), dehydration and coldness, and a delay in balanopreputial separation.***	Subjects who are breastfeeding, pregnant or planning a pregnancy during the course of the study are excluded. Additionally, all females of child-bearing potential must be taking adequate contraception during the study and have a negative pregnancy test prior to entry. See Section 5.1 for further details.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Given that albiglutide is an albumin-based protein therapeutic, it is likely to be transferred to breast milk. Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation.	
Accelerated sexual maturation in juveniles	Long-acting GLP-1R agonists have the potential to accelerate sexual maturation in monkeys based on absolute testes weight and similar trends in prostate, seminal vesicle, epididymides weights and histological assessment of maturity.	Subjects under 18 years of age are excluded (see Section 5.1).
Albiglutide matching placebo injections	Albiglutide placebo injections using the lyophilized DCC pen injector were associated with a clinically relevant rate of injection site reactions in the Phase III studies. There is no experience with placebo injections using the liquid auto-injector, including volume and pH differences from the lyophilized product placebo.	Subjects will be advised that when injecting in the same region, to use a different injection site each week. ***Risk communication via informed consent form for subjects.***

Section 5.2, Exclusion Criteria 5

Original text:

5. History of thyroid dysfunction or an abnormal (i.e., outside the normal reference range) thyroid function test assessed by thyroid stimulating hormone at screening.

Amended text:

5. Abnormal (i.e., outside the normal reference range) thyroid stimulating hormone (TSH) at screening.

Section 5.2, Exclusion Criteria 14, last sentence.

Original text:

14. eGFR ≤30 mL/min/1.73 m^2 (calculated using the MDRD formula) at screening.

    Note: As the use of metformin in subjects with varying degrees of renal function may differ from country to country, use of metformin should be in accordance with the metformin product label within the participating country.

    Fasting triglyceride level >750 mg/dL at screening.

Amended text:

14. eGFR ≤30 mL/min/1.73 m^2 (calculated using the MDRD formula) at screening.

    Note: As the use of metformin in subjects with varying degrees of renal function may differ from country to country, use of metformin should be in accordance with the metformin product label within the participating country.

    Etc……

24. Fasting triglyceride level >750 mg/dL at screening.

Section 5.2, Exclusion Criteria 21

Original text:

21. A positive pre-study drug/alcohol screen.

New text:

21. Positive urine alcohol/drug screen result at Screening, unless the subject is taking a medically approved medication for which a positive drug screen simply verifies the use of this medication

Section 5.2, Section 7, paragraph 4 and paragraph 5

New text:

Study visits between Baseline (Week 0) and End of treatment (Week 26) will have a visit window of ±3 days and the follow-up visit (Week 34) will have a visit window of ±7 days. If extraordinary events that make it impossible for subjects to complete a visit/dosing within the visit window (e.g., holidays, personal emergencies), the investigator should contact the medical monitor for advice.

If a subject misses a weekly scheduled visit for receiving albiglutide treatments, the albiglutide treatments should be administered as soon as possible within 3 days after the missed dose. Thereafter, subjects can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, the site staff should wait and administer at the subject's next regularly scheduled visit. If a subject misses 2 or more consecutive dosing, the investigator should contact the medical monitor to discuss options for helping assure better adherence. The medical monitor shall make a decision (on a case by case basis) on whether the subject should be withdrawn from the study.

Section 7.1, Time and Events Table HbA1c

Original text:

Procedure		Treatment													
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
	Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
HbA_{1c} [6,9]		X	X	X			X				X				

Amended text:

Procedure		Treatment													
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
	Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
HbA_{1c} [6,9]		X	X	X			X				X				*X*

Section 7.1, Time and Events Table PK Sampling

Original text:

Procedure		Treatment													
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
	Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
PK samples[10]															

Procedure		Treatment													End of Treatment[13,14]	Follow-up[15]
	Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
	Week	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**34**
PK samples[10]		X													X	

Amended text:

Procedure		Treatment													
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
	Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
PK samples[10]															X

Procedure		Treatment													End of Treatment[13,14]	Follow-up[15]
	Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
	Week	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**34**
PK samples[10]															X	

Section 7.6.1, Blood Sample Collection

Original text:

Approximately 2 mL of blood will be collected into 3mL di-potassium ethylenediaminetetraacetic acid (K_2-EDTA) tubes. The sample will be centrifuged in a refrigerated (4°C) centrifuge at 1500 x g for 15 minutes. The resulting plasma will be transferred into an appropriately labeled 1.8 or 2 mL polypropylene cryovial for albiglutide analysis. The tube must be frozen at -80°C within 60 minutes of collection.

Amended text:

Blood samples will be collected and stored as detailed in the Study Reference Manual (SRM).

Section 12.9.1.1, Handling of Missing Data, Examination of Missing Data Patterns

Original text:

Examination of Missing Data Patterns

It is expected that the pattern of missing data will be similar in both treatment arms given that each treatment arm is using the same drug but different formula.

To examine the nature of missing data, cohorts of subjects will be defined based on the scheduled assessments (HbA1c change from baseline) that were completed at Weeks 1, ***5, 9, 13, 17, 21,*** and 26.

- Subjects who have week 1 assessment only
- Subjects who have assessments up to and including ***Week 5*** only
- Subjects who have assessments up to and including ***Week 9*** only
- Subjects who have assessments up to and including ***Week 13*** only
- Subjects who have assessments up to and including ***Week 17*** only
- Subjects who have assessments up to and including ***Week 21*** only
- Subjects who have assessments up to and including Week 26.

The number and percentage of subjects on each treatment in the 7 cohorts defined here will be tabulated. Graphical methods will be used to examine changes from baseline over time to assess the pattern of outcomes prior to withdrawal.

Amended text:

Examination of Missing Data Patterns

It is expected that the pattern of missing data will be similar in both treatment arms given that each treatment arm is using the same drug but different formula.

To examine the nature of missing data, cohorts of subjects will be defined based on the scheduled assessments (HbA1c change from baseline) that were completed at Weeks ***1, 4, 8, 12, 16, 20, and 26.***

- Subjects who have week 1 assessment only
- Subjects who have assessments up to and including ***Week 4*** only
- Subjects who have assessments up to and including ***Week 8*** only
- Subjects who have assessments up to and including ***Week 12*** only
- Subjects who have assessments up to and including ***Week 16*** only
- Subjects who have assessments up to and including ***Week 20*** only
- Subjects who have assessments up to and including ***Week 26***.

The number and percentage of subjects on each treatment in the 7 cohorts defined here will be tabulated. Graphical methods will be used to examine changes from baseline over time to assess the pattern of outcomes prior to withdrawal.

Changes Resulting from Protocol Amendment 2

This amendment is applicable to all participating countries.

Summary of Changes

1. Protocol modified to allow subjects who discontinue investigational product to be followed for safety and efficacy unless the subject is “lost to follow-up” or withdraws consent.

2. Minor updates to benefit risk table

3. Clarification in inclusion criteria that those subjects on a stable dose of metforim must be receiving metformin as monotherapy.

4. Exclusion criteria relating to use of dipeptidyl peptidase-IV inhibitors updated to include GLP 1 receptor agonists and other antidiabetic medications.

5. Clarification of metformin dose adjustment.

6. Text relating to prohibited medications modified to provide details on dipeptidyl peptidase-IV inhibitors, GLP 1 receptor agonists and other antidiabetic medications.

7. Addition of visit windows to Time and Events Table.

8. Footnotes to Time and Events Table updated

9. Modifications made to the primary analysis, secondary analyses, supportive primary analyses, impact of missing data on primary analysis, and sensitivity analysis.

10. Minor typographical errors

Synopsis, analysis, primary analysis

Original text

HbA_{1c} change from baseline at Week 26 will be analyzed using a mixed-effect model with repeated measures (MMRM) in the intent-to-treat (ITT) population. MMRM will use all available data ***(including post-hyperglycemia rescue data).*** Non-inferiority testing will be performed at a one-sided alpha of 0.025 and non-inferiority margin of 0.4.

Amended text:

HbA_{1c} change from baseline at Week 26 will be analyzed using a mixed-effect model with repeated measures (MMRM) in the intent-to-treat (ITT) population. ***MMRM will use all available data, including post-hyperglycemia rescue data, and will include data from subjects who discontinue treatment. Imputation under the non-inferiority null hypothesis for missing data will be incorporated.*** Non-inferiority testing will be performed at a one-sided alpha of 0.025 and non-inferiority margin of 0.4.

Synopsis, analysis, secondary analyses, third paragraph

Original text

The secondary endpoint FPG change from baseline ***will be analyzed analogous to the primary endpoint HbA_{1c} using MMRM. Imputation for missing data will not be incorporated for the secondary endpoint FPG.***

Amended text:

The secondary endpoint FPG change from baseline ***at Week 26 will be analyzed using MMRM without imputation.***

Section 4.1, Figure 1, study schematic, footnote 2

Original text

2. Follow-up visit only for subjects who have discontinued ***study treatment (see Section 5.5) or subjects who have completed the 26 week treatment period,*** but do not consent and/or are not eligible to participate in the 26 week extension study (Study 204682).

Amended text:

2. Follow-up visit only for those subjects who discontinued ***investigational product (see Section 5.5), were withdrawn from the study, or who have completed the 26 week treatment period,*** but do not consent and/or are not eligible to participate in the 26 week extension study (Study 204682).

Section 4.1, Overall Design, fourth bullet point

Original text

- During the screening period, subjects will provide written informed consent and undergo procedures to determine eligibility for study participation. (Time and Events Table Section 4).

Amended text:

- During the screening period, subjects will provide written informed consent and undergo procedures to determine eligibility for study participation. ***Screening will occur within 2 weeks of randomization.*** (Time and Events Table Section 7.1).

Section 4.1, Overall Design, last bullet point

Original text

- Subjects who complete the 26 week treatment period and meet all eligibility criteria may consent to participate in Study 204682, a 26 week extension study.

Amended text:

- Subjects, who completed the 26 week treatment period, ***did not discontinue investigational product,*** and meet all eligibility criteria may consent to participate in Study 204682, a 26 week extension study.

Section 4.2, Treatment Arms and Duration, penultimate point

Original text

- Down-titration (dose reduction) of albiglutide from 50 mg to 30 mg is **NOT** permitted (see Section 4.4). If a subject experiences tolerability issues with the higher 50mg dose then the subject may ***be withdrawn from the study at the discretion of the investigator.***

Amended text:

- Down-titration (dose reduction) of albiglutide from 50 mg to 30 mg is **NOT** permitted (see Section 4.4). If a subject experiences tolerability issues with the higher 50mg dose then the subject may ***discontinue investigational product (at the discretion of the investigator) and will be followed for safety and efficacy.***

Section 4.6.1, Table 2, Risk Assessment for Albiglutide

Original text:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) (albiglutide [GSK716155]) Identified Risks		
Pancreatitis	Acute pancreatitis has been reported in association with albiglutide and other GLP-1 receptor agonists in clinical trials and during postmarketing experience. Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether they are at increased risk for pancreatitis.	Subjects with a history of acute or chronic pancreatitis are excluded from entering the study (See Section 5.2). Subjects will be informed of the characteristic symptom of pancreatitis: persistent severe abdominal pain. If pancreatitis is suspected, albiglutide should be promptly discontinued and if pancreatitis is confirmed, study treatment will not be restarted (see Section 5.5). Risk communication via guidance for investigators ***(see Section 6 of the IB***) and informed consent form for subjects.
Gastrointestinal (GI) events.	Albiglutide has not been studied in subjects with severe GI disease, including severe gastroparesis. Use of albiglutide can be associated with GI side effects such as diarrhea, nausea, and vomiting.	Subjects with severe gastroparesis are excluded from entering the study (See Section 5.2). Subjects with a history of significant GI surgery that in the opinion of the investigator is likely to significantly affect upper GI or pancreatic function are excluded from entering the study (See Section 5.2). Risk communication via guidance for investigators ***(see Section 6 of the IB)*** and informed consent form for subjects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypoglycemia.	Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycemia when used as monotherapy or in combination with agents such as metformin which also have low intrinsic risk for significant hypoglycemia.	To reduce the risk of hypoglycemia when starting albiglutide all subjects are required to have HbA1c ≥7.0 at screening (see Section 5.1). Subjects are neither allowed to use insulin nor insulin secretagogues during the ***study. Except*** as part of hyperglycemia rescue (see Section 5.4) Risk communication via guidance for investigators ***(see Section 6 of the IB)*** and informed consent form for subjects.
Immunogenicity (e.g., including anti-drug antibodies, clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, and other potential immune-related AEs).	Risk assessment of the albiglutide molecule predicted low immunogenic potential, which was substantiated for the commercial lyophilized DCC pen injector product in the registration program. Treatment-emergent anti-drug antibodies were detected in ~5% subjects over studies of up to 3 years duration and were generally transient, of low titer, and not neutralizing. Subjects who tested positive for anti-albiglutide antibodies experienced a similar glycemic response (HbA1c and fasting plasma glucose) to those who did not test positive for antibodies. Other than injection site reactions (see below), the overall safety profile appeared similar among the subset of subjects who did and those who did not test positive for anti-albiglutide antibodies. Changes in the propensity of the liquid product to form aggregates could have an impact on anti-drug antibody characteristics or immune related AEs. However, the likelihood of clinically important changes in anti-drug antibody characteristics or immune related AEs with the liquid albiglutide drug product compared to the lyophilized drug product is considered low based on the absence of substantive qualitative differences between formulations.	A pre-exposure baseline serum sample will be taken and tested for pre-existing ADAs. The development of anti-albiglutide antibodies will be assessed as part of this study.
Hypersensitivity Reactions	Systemic allergic/hypersensitivity reactions are of potential concern with any injected protein and were reported rarely	Subjects with a known allergy to albiglutide or any product components (including yeast and human albumin) are

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	in the Phase III program with lyophilized albiglutide. Data have not demonstrated an association of albiglutide with an increased incidence of anaphylaxis, angioedema, or urticaria. However, there was one non-serious hypersensitivity event (rash and itching associated with dyspnea upon rechallenge) that was consistent with a possible albiglutide-related systemic hypersensitivity reaction in a female subject who was anti-albiglutide antibody negative. ***See Section 5.4 of the IB.***	excluded from the study (See Section 5.2). Subjects will be informed of the symptoms of severe hypersensitivity or allergy and be advised to seek medical assistance immediately. Risk communication via guidance for investigators ***(see Section 6 of the IB***) and informed consent form for subjects.
Injection site reactions (ISRs)	Albiglutide injections may cause rash, erythema or itching and/or other reactions at the site of injection. In the Phase III program with the lyophilized drug product, most subjects with ISRs did not test positive for anti-albiglutide antibodies. However, injection site reactions were reported more frequently among those who did test positive for anti-albiglutide antibodies (41% of the ADA positive subjects reported one or more injection site reactions) than among those who were consistently antibody negative (14% of the antidrug antibody negative subjects reported one or more injection site reactions). Overall, for albiglutide, injection site reactions have not been associated with clinically significant sequelae; although they can be a tolerability issue and were the most common reason for withdrawal of study medication for subjects (approximately 2.0%) in the albiglutide group. Differences between formulation characteristics (e.g. lower pH and larger volume for the 50 mg dose of the liquid formulation) may impact the injection site reaction profile.	Subjects will be advised that when injecting in the same region, to use a different injection site each week. Risk communication via guidance for investigators ***(see Section 6 of the IB)*** and informed consent form for subjects. The development of injection site reactions will be assessed as part of this study.
Other adverse reactions (e.g., pneumonia, atrial fibrillation/atrial flutter, and appendicitis)	In the Phase III program in T2DM, other possible albiglutide related adverse reactions were identified. These events occurred at a cumulative incidence <3% in studies up to 3 years in duration. These events were reported more frequently with albiglutide than comparators. ***See***	Risk communication via guidance for investigators ***(see Section 6 of the IB)*** and informed consent form for subjects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Section 5.4 of the IB.	
Investigational Product (IP) (albiglutide [GSK716155]) Potential Risks		
Thyroid C-cell tumors	GLP-1 receptor agonists, including albiglutide increase serum calcitonin in rodents and other GLP-1 receptor agonists are associated with thyroid C-cell focal hyperplasia and C-cell tumors in rodents It is unknown whether GLP-1 receptor agonists are associated with thyroid C-cell tumors in humans, including medullary thyroid cancer (MTC).	Subjects with a personal or family history of MTC or subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) are excluded from the study (See Section 5.2). Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. Routine monitoring of serum calcitonin is not recommended. However, if serum calcitonin is found to be elevated the subject should be referred to a specialist for further evaluation. If MTC or other thyroid C-cell neoplasia is diagnosed, study treatment will be discontinued (see Section 5.5).
Other malignant neoplasms	Theoretical concerns have been raised regarding use of incretin based therapies and other malignancies such as pancreatic cancer [Egan, 2014] and malignancy when used in combination with insulin based on hypotheses of biological plausibility [European Public Assessment Report, 2014], and hematological malignancies [FDA Summary Basis of Approval, 2014].	Relevant data on pancreatic cancer are summarized in ***IB Section 5.4.*** Subjects with a history of cancer that has not been in full remission for at least 3 years before screening are excluded from the study (See Section 5.2).
Cardiovascular (CV) safety of antidiabetic therapy	T2DM is associated with an elevated risk of CV disease. Global regulatory agencies require new antidiabetic therapies to demonstrate that the new therapy is not associated with an unacceptable increase in CV risk. In the Phase III registration program, an independent Clinical Endpoint Committee prospectively adjudicated blinded CV events. The final CV meta-analysis showed no increased CV risk (MACE [major adverse cardiovascular event] + composed of CV death, myocardial infarction [MI], stroke, and hospitalization for unstable angina) with albiglutide versus all comparators (MACE+ hazard ratio =	Relevant data on cardiovascular events are summarized ***in IB Section 5.4.*** Subjects with clinically significant CV and/or cerebrovascular disease within 3 months before screening will be excluded from the study. Further details are provided in Section 5.2. ***Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects***

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	1.00; 95% CI: 0.68, 1.49). See Section 5.4 of the IB.	
Hepatotoxicity	Hepatotoxicity is an area of interest in drug development. Patients with T2DM are at increased risk for liver enzyme abnormalities and disease related liver conditions. One subject treated with albiglutide in the Phase III clinical program developed probable drug induced liver injury with an asymptomatic elevation in alanine amino transferase (ALT) and total bilirubin although the cases had some atypical features and complicating factors .	Routine liver safety laboratory evaluations will be conducted and specific withdrawal criteria for elevated liver function tests have been defined (See Section 5.5.4).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) (albiglutide [GSK716155]) Additional Considerations		
Subject population with severe renal impairment (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2)	Experience in T2DM subjects with severe renal impairment is limited (in the Phase III programme a total of 19 subjects with eGFR <30 mL/min/1.73m^2 received albiglutide). In a Phase III study of patients with varying degrees of renal impairment, in the albiglutide group, on-therapy GI AEs occurred with a higher incidence and higher event rate in subjects with moderate and severe renal impairment compared to those with mild renal impairment. GI events may lead to dehydration and worsen renal function.	Subjects with an eGFR ≤30 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease (MDRD) formula) are excluded from the study (see Section 5.2). Risk communication via guidance for investigators (see Section 5.4and ***Section 6 of the IB)*** and informed consent form for subjects.
Drug interactions	Albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the development program, drug interactions studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant PK or PD effects.	Investigators will be advised to take the effect of albiglutide on gastric emptying into account when prescribing concomitant medication.
Fetal & neonatal developmental toxicity	Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Albiglutide administration during the major period of organogenesis in female mice resulted in embryofetal lethality, and bent/wavy ribs in the fetus at 50 mg/kg/day. Offspring of mice dosed with 50 mg/kg/day during organogenesis had reduced pre-weaning body weight (which recovered after weaning), dehydration and coldness, and a delay in balanopreputial separation. Given that albiglutide is an albumin-based protein therapeutic, it is likely to be transferred to breast milk. Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation.	Subjects who are breastfeeding, pregnant or planning a pregnancy during the course of the study are excluded. Additionally, all females of child-bearing potential must be taking adequate contraception during the study and have a negative pregnancy test prior to entry. See Section 5.1 for further details.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Accelerated sexual maturation in juveniles	Long-acting GLP-1R agonists have the potential to accelerate sexual maturation in monkeys based on absolute testes weight and similar trends in prostate, seminal vesicle, epididymides weights and histological assessment of maturity.	Subjects under 18 years of age are excluded (see Section 5.1).
Study Procedures		
Albiglutide matching placebo injections	Albiglutide placebo injections using the lyophilized DCC pen injector were associated with a clinically relevant rate of injection site reactions in the Phase III studies. There is no experience with placebo injections using the liquid auto-injector, including volume and pH differences from the lyophilized product placebo.	Subjects will be advised that when injecting in the same region, to use a different injection site each week. Risk communication via informed consent form for subjects.

Amended text

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) (albiglutide [GSK716155]) Identified Risks		
Pancreatitis	Acute pancreatitis has been reported in association with albiglutide and other GLP-1 receptor agonists in clinical trials and during postmarketing experience. Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether they are at increased risk for pancreatitis.	Subjects with a history of acute or chronic pancreatitis are excluded from entering the study (See Section 5.2). Subjects will be informed of the characteristic symptom of pancreatitis: persistent severe abdominal pain. If pancreatitis is suspected, albiglutide should be promptly discontinued and if pancreatitis is confirmed, study treatment will not be restarted (see Section 5.5). Risk communication via guidance for investigators ***(see albiglutide IB)*** and informed consent form for subjects.
Gastrointestinal (GI) events.	Albiglutide has not been studied in subjects with severe GI disease, including severe gastroparesis. Use of albiglutide can be associated with GI side effects such as diarrhea, nausea, and vomiting.	Subjects with severe gastroparesis are excluded from entering the study (See Section 5.2). Subjects with a history of significant GI surgery that in the opinion of the investigator is likely to significantly affect upper GI or pancreatic function are excluded from entering the study (See Section 5.2). Risk communication via guidance for investigators ***(see albiglutide IB***) and informed consent form for subjects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypoglycemia.	Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycemia when used as monotherapy or in combination with agents such as metformin which also have low intrinsic risk for significant hypoglycemia.	To reduce the risk of hypoglycemia when starting albiglutide all subjects are required to have HbA1c ≥7.0 at screening (see Section 5.1). Subjects are neither allowed to use insulin nor insulin secretagogues during the ***study except*** as part of hyperglycemia rescue (see Section 5.4) Risk communication via guidance for investigators ***(see the albiglutide IB)*** and informed consent form for subjects.
Immunogenicity (e.g., including anti-drug antibodies, clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, and other potential immune-related AEs).	Risk assessment of the albiglutide molecule predicted low immunogenic potential, which was substantiated for the commercial lyophilized DCC pen injector product in the registration program. Treatment-emergent anti-drug antibodies were detected in ~5% subjects over studies of up to 3 years duration and were generally transient, of low titer, and not neutralizing. Subjects who tested positive for anti-albiglutide antibodies experienced a similar glycemic response (HbA1c and fasting plasma glucose) to those who did not test positive for antibodies. Other than injection site reactions (see below), the overall safety profile appeared similar among the subset of subjects who did and those who did not test positive for anti-albiglutide antibodies. Changes in the propensity of the liquid product to form aggregates could have an impact on anti-drug antibody characteristics or immune related AEs. However, the likelihood of clinically important changes in anti-drug antibody characteristics or immune related AEs with the liquid albiglutide drug product compared to the lyophilized drug product is considered low based on the absence of substantive qualitative differences between formulations.	A pre-exposure baseline serum sample will be taken and tested for pre-existing ADAs. The development of anti-albiglutide antibodies will be assessed as part of this study. ***Risk communication via guidance for investigators (see albiglutide IB) and informed consent form for the subject.***
Hypersensitivity Reactions	Systemic allergic/hypersensitivity reactions are of potential concern with any injected protein and were reported rarely	Subjects with a known allergy to albiglutide or any product components (including yeast and human albumin) are

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	in the Phase III program with lyophilized albiglutide. Data have not demonstrated an association of albiglutide with an increased incidence of anaphylaxis, angioedema, or urticaria. However, there was one non-serious hypersensitivity event (rash and itching associated with dyspnea upon rechallenge) that was consistent with a possible albiglutide-related systemic hypersensitivity reaction in a female subject who was anti-albiglutide antibody negative. See ***albiglutide IB.***	excluded from the study (See Section 5.2). Subjects will be informed of the symptoms of severe hypersensitivity or allergy and be advised to seek medical assistance immediately. Risk communication via guidance for investigators ***(see albiglutide IB)***) and informed consent form for subjects.
Injection site reactions (ISRs)	Albiglutide injections may cause rash, erythema or itching and/or other reactions at the site of injection. In the Phase III program with the lyophilized drug product, most subjects with ISRs did not test positive for anti-albiglutide antibodies. However, injection site reactions were reported more frequently among those who did test positive for anti-albiglutide antibodies (41% of the ADA positive subjects reported one or more injection site reactions) than among those who were consistently antibody negative (14% of the antidrug antibody negative subjects reported one or more injection site reactions). Overall, for albiglutide, injection site reactions have not been associated with clinically significant sequelae; although they can be a tolerability issue and were the most common reason for withdrawal of study medication for subjects (approximately 2.0%) in the albiglutide group. Differences between formulation characteristics (e.g. lower pH and larger volume for the 50 mg dose of the liquid formulation) may impact the injection site reaction profile.	Subjects will be advised that when injecting in the same region, to use a different injection site each week. Risk communication via guidance for investigators ***(see albiglutide IB)*** and informed consent form for subjects. The development of injection site reactions will be assessed as part of this study ***where the investigator or designee will administer both the albiglutide liquid drug product and the albiglutide lyophilized drug product.***
Other adverse reactions (e.g., pneumonia, atrial fibrillation/atrial flutter, and appendicitis)	In the Phase III program in T2DM, other possible albiglutide related adverse reactions were identified. These events occurred at a cumulative incidence <3% in studies up to 3 years in duration. These events were reported more frequently with albiglutide than comparators. ***See***	Risk communication via guidance for investigators ***(see albiglutide IB)*** and informed consent form for subjects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	albiglutide IB.	
Investigational Product (IP) (albiglutide [GSK716155]) Potential Risks		
Thyroid C-cell tumors	GLP-1 receptor agonists, including albiglutide increase serum calcitonin in rodents and other GLP-1 receptor agonists are associated with thyroid C-cell focal hyperplasia and C-cell tumors in rodents It is unknown whether GLP-1 receptor agonists are associated with thyroid C-cell tumors in humans, including medullary thyroid cancer (MTC).	Subjects with a personal or family history of MTC or subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) are excluded from the study (See Section 5.2). Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines. Routine monitoring of serum calcitonin is not recommended. However, if serum calcitonin is found to be elevated the subject should be referred to a specialist for further evaluation. If MTC or other thyroid C-cell neoplasia is diagnosed, study treatment will be discontinued (see Section 5.5).
Other malignant neoplasms	Theoretical concerns have been raised regarding use of incretin based therapies and other malignancies such as pancreatic cancer [Egan, 2014] and malignancy when used in combination with insulin based on hypotheses of biological plausibility [European Public Assessment Report, 2014], and hematological malignancies [FDA Summary Basis of Approval, 2014].	Relevant data on pancreatic cancer are summarized in ***the albiglutide IB.*** Subjects with a history of cancer that has not been in full remission for at least 3 years before screening are excluded from the study (See Section 5.2). ***A history of squamous cell or basal cell carcinoma of the skin or treated cervical intra-epithelial neoplasia I or II is allowed.***
Cardiovascular (CV) safety of antidiabetic therapy	T2DM is associated with an elevated risk of CV disease. Global regulatory agencies require new antidiabetic therapies to demonstrate that the new therapy is not associated with an unacceptable increase in CV risk. In the Phase III registration program, an independent Clinical Endpoint Committee prospectively adjudicated blinded CV events. The final CV meta-analysis showed no increased CV risk (MACE [major adverse cardiovascular event] + composed of CV death, myocardial infarction [MI], stroke, and hospitalization for unstable angina) with	Relevant data on cardiovascular events are summarized in IB Section 5.4. Subjects with clinically significant CV and/or cerebrovascular disease within 3 months before screening will be excluded from the study. Further details are provided in Section 5.2

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	albiglutide versus all comparators (MACE+ hazard ratio = 1.00; 95% CI: 0.68, 1.49). See Section 5.4 of the IB.	
Hepatotoxicity	Hepatotoxicity is an area of interest in drug development. Patients with T2DM are at increased risk for liver enzyme abnormalities and disease related liver conditions. One subject treated with albiglutide in the Phase III clinical program developed probable drug induced liver injury with an asymptomatic elevation in alanine amino transferase (ALT) and total bilirubin although the cases had some atypical features and complicating factors .	Routine liver safety laboratory evaluations will be conducted and specific withdrawal criteria for elevated liver function tests have been defined (See Section 5.5.4).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) (albiglutide [GSK716155]) Additional Considerations		
Subject population with severe renal impairment (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2)	Experience in T2DM subjects with severe renal impairment is limited (in the Phase III programme a total of 19 subjects with eGFR <30 mL/min/1.73m^2 received albiglutide). In a Phase III study of patients with varying degrees of renal impairment, in the albiglutide group, on-therapy GI AEs occurred with a higher incidence and higher event rate in subjects with moderate and severe renal impairment compared to those with mild renal impairment. GI events may lead to dehydration and worsen renal function.	Subjects with an eGFR ≤30 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease (MDRD) formula) are excluded from the study (see Section 5.2). Risk communication via guidance for investigators ***(see albiglutide IB)*** and informed consent form for subjects.
Drug interactions	Albiglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the development program, drug interactions studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin which demonstrated no clinically relevant PK or PD effects.	Investigators will be advised to take the effect of albiglutide on gastric emptying into account when prescribing concomitant medication.
Fetal & neonatal developmental toxicity	Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Albiglutide administration during the major period of organogenesis in female mice resulted in embryofetal lethality, and bent/wavy ribs in the fetus at 50 mg/kg/day. Offspring of mice dosed with 50 mg/kg/day during organogenesis had reduced pre-weaning body weight (which recovered after weaning), dehydration and coldness, and a delay in balanopreputial separation. Given that albiglutide is an albumin-based protein therapeutic, it is likely to be transferred to breast milk. Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation.	Subjects who are breastfeeding, pregnant or planning a pregnancy during the course of the study are excluded. Additionally, all females of child-bearing potential must be taking adequate contraception during the study and have a negative pregnancy test prior to entry. See Section 5.1 for further details. ***Risk communication via guidance for investigators (see albiglutide IB) and informed consent form for subjects.***

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Accelerated sexual maturation in juveniles	Long-acting GLP-1R agonists have the potential to accelerate sexual maturation in monkeys based on absolute testes weight and similar trends in prostate, seminal vesicle, epididymides weights and histological assessment of maturity.	Subjects under 18 years of age are excluded (see Section 5.1).
Study Procedures		
Albiglutide matching placebo injections	Albiglutide placebo injections using the lyophilized DCC pen injector were associated with a clinically relevant rate of injection site reactions in the Phase III studies. There is no experience with placebo injections using the liquid auto-injector, including volume and pH differences from the lyophilized product placebo.	Subjects will be advised that when injecting in the same region, to use a different injection site each week. Risk communication via informed consent form for subjects.

Section 5.1 Inclusion Criteria 2

Original text

2. Historical diagnosis of T2DM (at least 3 months), experiencing inadequate glycemic control on current regimen of diet and exercise or on a stable ***maximal tolerated dose of metformin***, maintained for approximately 8 weeks prior to screening.

Amended text:

2. Historical diagnosis of T2DM (at least 3 months), experiencing inadequate glycemic control on current regimen of diet and exercise or on a stable ***dose of metformin of at least 1500 mg or the documented maximal tolerated dose if less than 1500 mg metformin (monotherapy),*** maintained for approximately 8 weeks prior to screening

Section 5.2 Exclusion Criteria 14

Original text

14. eGFR ≤30 mL/min/1.73 m^2 (calculated using the MDRD formula) at screening.

    Note: ***As the use of metformin in subjects with varying degrees of renal function may differ from country to country, use of metformin should be in accordance with the metformin product label within the participating country.***

Amended text:

25. eGFR ≤30 mL/min/1.73 m^2 (calculated using the MDRD formula) at screening.

    Note: ***The use of metformin in subjects with varying degrees of renal function should be in accordance with the metformin product label.***

Section 5.2 Exclusion Criteria 18

Original text

18. Use of dipeptidyl peptidase-IV inhibitors within the 3 months before randomization.

Amended text:

18. Use of GLP 1 receptor agonists at any time. Use of dipeptidyl peptidase-IV inhibitors within the 3 months before randomization. ***Use of any other antidiabetic medications with the exception of metformin within 3 weeks before randomization.***

Section 5.5 Withdrawal/Stopping Criteria

Original text

5.5 Withdrawal/Stopping Criteria

Every effort should be made to keep subjects in the study. ***The reason for a subject not completing the study will be recorded in the subject's electronic case report form (eCRF).***

Any subject experiencing the following will be required to discontinue investigational product and will be withdrawn from the study:

- Any AE, which, in the opinion of the investigator precludes effective participation of the subject or poses a safety concern
- The following AEs **will *require withdrawal:***
    - Confirmed pancreatitis, acute or chronic.
    - Pancreatic cancer.
    - Confirmed MTC or other thyroid C-cell neoplasia.
    - Liver chemistry abnormalities exceeding the threshold criteria outlined in Section 5.5.4
    - QTc abnormalities exceeding the threshold criteria outlined in Section 5.5.5.
    - Severe allergic/hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology.
- eGFR ≤30 mL/min/1.73 m^2 (calculated using the MDRD formula).
- Subject becomes pregnant or intends to become pregnant during the study.
- Need for chronic use of a prohibited concomitant medication (Section 6.10.2)
- Major protocol deviation (the investigator should discuss the protocol deviation with the medical monitor before withdrawing study medication)
- Subject decision (reason to be documented in the eCRF, if specified by the subject)
- Investigator discretion
- Study closed/terminated or investigator site closed (where subject transfer to another site is not possible)

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must 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.
- In cases where the subject is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record.

- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

Subjects who are withdrawn or discontinue active participation in the study will no longer receive the randomized study treatment. Immediately upon discontinuation from active participation in this study, these subjects should complete the assessments as per the end of treatment clinic visit and return for the post-treatment follow-up clinic visit 8 weeks later (Section 7.1). If a subject is unable or unwilling to return for the follow-up assessments, every effort will be made to follow-up with the subject.

Withdrawn subjects will not be replaced.

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Amended text:

5.5 Withdrawal/Stopping Criteria

Every effort should be made to keep subjects in the study. ***The reason for a subject discontinuing investigational product or withdrawing from the study will be recorded in the subject's electronic case report form (eCRF).***

5.5.1 Permanent Discontinuation of Investigational Product

A subject may permanently discontinue investigational product at any time at his/her own request, or at the discretion of the investigator for safety or compliance reasons. A subject must permanently discontinue investigational product for the pre-specified reasons below.

- Any AE, which, in the opinion of the investigator precludes effective participation of the subject or poses a safety concern
- The following AEs **will** require ***discontinuation from investigational product:***
    - Confirmed pancreatitis, acute or chronic.
    - Pancreatic cancer.
    - Confirmed MTC or other thyroid C-cell neoplasia.
    - Liver chemistry abnormalities exceeding the threshold criteria outlined in Section 5.5.4
    - QTc abnormalities exceeding the threshold criteria outlined in Section 5.5.5.
    - Severe allergic/hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology.

- eGFR ≤30 mL/min/1.73 m^2 (calculated using the MDRD formula).
- Subject becomes pregnant or intends to become pregnant during the study.
- Need for chronic use of a prohibited concomitant medication (Section 6.10.2)
- Major protocol deviation (the investigator should discuss the protocol deviation with the medical monitor before withdrawing study medication)
- Subject decision (reason to be documented in the eCRF, if specified by the subject)
- Investigator discretion
- Study closed/terminated or investigator site closed (where subject transfer to another site is not possible)

In all cases, the reasons for investigational product discontinuation and the date of the last dose will be recorded in the subject's electronic case report form (eCRF) and the subject will continue in the study as described in 5.5.1.1.

5.5.1.1 Procedures for Subject Follow-up Following Discontinuation of Investigational Product

Subjects will be educated on the importance of remaining in the study and attending all scheduled study visits.

Subjects who permanently discontinue investigational product will be expected to attend clinic visits every 4 weeks through the End of Treatment visit, according to the study visit schedule, unless consent is actively withdrawn. Complete details are provided in the Time and Events Table (Section 7.1).

If a subject is unable or unwilling to continue attending clinic visits in person, other subject follow-up options to collect subject information as detailed in the informed consent (e.g., telephone calls, letters, review of subjects medical records) should be pursued.

5.5.2 Subjects Who Fail to Attend Clinic Visits

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must 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.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.5.3 Withdrawal from Study

Every effort should be made to keep subjects in the study. For subjects that choose to withdraw consent or are lost to follow up, the reason for not completing the study will be recorded in the subject's eCRF. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Subjects who are withdrawn or discontinue active participation in the study will no longer receive the randomized study treatment. Immediately upon discontinuation from active participation in this study, these subjects should complete the assessments as per the end of treatment clinic visit and return for the post-treatment follow-up clinic visit 8 weeks later (Section 7.1). If a subject is unable or unwilling to return for the follow-up assessments, every effort will be made to follow-up with the subject.

Withdrawn subjects will not be replaced.

Section 5.5.5 QTC Stopping Criteria, 3rd bullet.

Original text

- A subject who meets the following criteria ***will be withdrawn from the study***:

Amended text:

- A subject who meets the following criteria ***will discontinue investigational product***:

Section 6.3 Planned Dose Adjustments, 2nd paragraph.

Original text

- Down-titration (dose reduction) of albiglutide from 50 mg to 30 mg is **NOT** permitted (see Section 4.4). If a subject experiences tolerability issues with the higher 50mg dose then the subject may ***be withdrawn from the study at the discretion of the investigator.***

Amended text:

- Down-titration (dose reduction) of albiglutide from 50 mg to 30 mg is **NOT** permitted. If a subject experiences tolerability issues with the higher 50mg dose then the subject may ***discontinue investigational product (at the discretion of the investigator) and be followed for safety and efficacy.***

Section 6.3 Planned Dose Adjustments, 3rd paragraph.

Original text

Subjects on a stable dose of metformin at the start of the study may have their metformin dose adjusted at the discretion of the investigator based on clinical need.

Amended text:

The use of metformin in subjects with varying degrees of renal function should be in accordance with the metformin product label. It is encouraged that a stable metformin dose is maintained during the study. However the metformin dose may be downtitrated based on clinical need at the discretion of the investigator. Up-titration of metformin is permitted for subjects who require hyperglycemic rescue and metformin is selected as the rescue medication.

Section 6.4 Blinding, penultimate bullet.

Original text

- ***A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.***

Amended text:

- ***If the subject's treatment code is unblinded by the investigator or treating physician the subject will continue to receive treatment unless they meet one of the investigational product discontinuation or study withdrawal criteria outlined in Section 5.5***

Section 7 Study Assessments and Procedures, last sentence.

Original text

The medical monitor shall make a decision (on a case by case basis) on whether the subject should ***be withdrawn from the study.***

Amended text:

The medical monitor shall make a decision (on a case by case basis) on whether the subject should ***continue to receive investigation product.***

Table 4 Study Assessments, footnote 15

Original text

15. Follow-up visit for subjects ***who have discontinued study treatment (see Section 5.5)*** or subjects who have completed the 26 week treatment period, but do not consent and/or are not eligible to participate in the 26 week extension study (Study 204682).

Amended text:

15. Follow-up visit for those subjects ***who have stopped investigational product (see Section 5.5), withdrawn from the study*** or who have completed the 26 week treatment period, but do not consent and/or are not eligible to participate in the 26 week extension study (Study 204682).

Table 4 Schedule of Assessments, footnote 5

Footnote removed

Urine samples should be collected in the early morning.

Table 4 Schedule of Assessments, footnote 16

Footnote added

All visits will have a treatment window as in the table> Subjects will not be considered out of compliance if visit windows extend because of extraordinary events that make it impossible for subjects to complete a visit within the above window (e.g., holidays, vacations, personal emergencies). Determination of the maximum visit window deviation is at the discretion of the medical monitor

Table 4 Schedule of Assessments

Original text

Procedure		Treatment													End of Treatment[13,14]	Follow-up[15]
	Visit	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
	Week	13	14	15	16	17	18	19	20	21	22	23	24	25	26	34

Procedure		Treatment													End of Treatment[13,14]	Follow-up[15]
	Visit	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
	Week	13	14	15	16	17	18	19	20	21	22	23	24	25	26	34

Amended text

Procedure		Treatment													
	Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Week	-2	0	1	2	3	4	5	6	7	8	9	10	11	12
	Visit Window	**-14d**	**0d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**

Procedure		Treatment													End of Treatment[1] [3,14]	Follow-up[15]
	Visit	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
	Week	13	14	15	16	17	18	19	20	21	22	23	24	25	26	34
	Visit Window	***±3d***	***±3d***	***±3d***	***±3d***	***±3d***	***±3d***	***±3d***	***±3d***	***±3d***	***±3d***	***±3d***	***±3d***	***±3d***	***±3d***	***±7d***

Table 5 Study Assessments for Subjects Who Permanently Discontinue Investigational Product

New text

Table 5 Schedule of Assessments for Subjects Who Permanently Discontinue Investigational Product

Procedure	**Continue Scheduled Clinic Visit (Weeks 4, 8, 12, 16, 20) [4,5]**	**Week 26 (Equivalent to End of Treatment Visit)**	**Follow-up Week 34**
Full (F) or brief (B) physical exam	B	F	F
Weight	X	X	X
12-lead ECG [1]		X	X
Vital Signs	X	X	X
Clinical chemistry/hematology samples[2]	X	X	X
HbA1c and FPG [3]	X	X	X
Review AE/SAE, concomitant medication and hypoglycemia events	X	X	X

1. 12-lead ECGs will be obtained **before** measurement of vital signs and collection of blood samples for laboratory testing. Vital signs measurement will be taken before collection of blood samples. See Section 7.4.5.
2. Clinical chemistry and hematology assessments are described in Section 7.4.6.
3. Subjects will have their FPG and HbA_{1c} levels evaluated to monitor for potential hyperglycemia.
4. Week will be dependent on when the subject discontinues investigational product. Subjects will start this schedule as soon as possible following investigational product discontinuation and timings of visits will be the same as for if the subject was continuing on investigational product. The timing of the clinic visits can be modified at the discretion of the investigator. All subjects must attend the Week 26 visit.
5. Additional unscheduled visits will occur as medically necessary

Section 7.4.1.5 AEs of Special Interest, last paragraph

Original text

Subjects with drug hypersensitivity reactions that are not reasonably attributable to another cause or pancreatitis should be ***withdrawn from the study*** and should not be rechallenged with albiglutide (see Section 5.5 for complete list of AEs of special interest requiring withdrawal).

Amended text:

Subjects with drug hypersensitivity reactions that are not reasonably attributable to another cause or pancreatitis ***should discontinue investigational product*** and should not be rechallenged with albiglutide (see Section 5.5 for complete list of AEs of special interest requiring withdrawal).

Section 7.4.3. Physical Exams, penultimate sentence

Original text

Weight will be measured ***at each clinic visit.***

Amended text:

Weight will be measured ***at the time points specified in the Time and Events Table Section 7.1***

Section 7.4.6. Clinical Safety Laboratory Assessments, penultimate paragraph, last scentence

Original text

The results of the test must be entered into the eCRF.

Amended text:

HbA_{1c} results from a local laboratory must be entered into the eCRF.

Section 9.4 Key Elements of Analysis Plan

Original text

9.4 Key Elements of Analysis Plan

9.4.1 Primary Analyses

The primary endpoint is the change from baseline in HbA1c at Week 26. The primary analysis of the primary endpoint will be conducted using a mixed-effect model with repeated measures (MMRM) in the ITT Population. MMRM will use all available data (including post-hyperglycemia rescue data). Analysis excluding post-rescue HbA1c data will also be performed as supportive and is described in Section 9.4.5.

The model will include HbA1c change from baseline at all post-baseline visits as dependent variables; treatment, region, age category, weight, background antidiabetic therapy, visit week, and treatment-by-week interaction as fixed effects; baseline HbA1c as a continuous covariate; and subject as a random effect. Treatment effects estimates (and associated CI) of albiglutide liquid drug product will be evaluated within this MMRM model as least squares means contrasts relative to the lyophilized drug product. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion.

The primary analysis will include all HbA1c values collected at scheduled visits up to

Week 26. This will include values after hyperglycemia rescue. Missing data, in the context of the primary analysis at Week 26, refer to those cases where the Week 26 HbA1c value is not available or was not collected.

The primary endpoint HbA1c change from baseline at Week 26 may also be analyzed using the same MMRM model in the PP Population if needed as a supportive analysis.

Special attention will be paid to the handling of missing data in statistical analysis. Although, it is expected that the pattern of missing data will be similar in both treatment arms given that the treatment arms are the same drug but different formulations. The method for the primary analysis, MMRM, assumes missing at random. The sensitivity of the results of analysis to the method of handling missing values will be investigated, especially if the number of missing values is substantial or if the characteristics of missing values differ between treatment groups. Further details of the sensitivity analysis, including imputation methods and assumptions about the missing data are described in Section 9.4.5.4.

9.4.2 Secondary Analyses

The evaluation of the safety and tolerability as assessed by immunogenicity and ISRs of albiglutide liquid drug product and the lyophilized drug product will be provided by reporting the event rates, and the associated 95% CI.

The overall general safety and tolerability of albiglutide liquid drug product versus lyophilized drug product will be evaluated in tabular and/or graphical format and summarized descriptively.

AEs and SAEs, physical examinations, clinical laboratory evaluations, vital sign measurements, and 12-lead electrocardiogram will be summarized by treatment group. For continuous variables, these summaries will include sample size, mean, median, standard deviation (and/or standard error), minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. The exposure-adjusted incidence rate will also be calculated as the number of events in a given period divided by the total person time on treatment of subjects at risk within the same period. The exposure-adjusted incidence rate will be expressed as an annualized rate expected. No inferential testing will be performed on the safety variables.

Hypoglycemic events will be analyzed separately from other AEs. All hypoglycemic events will be classified as severe, documented symptomatic, asymptomatic, probable symptomatic, and pseudohypoglycemia, as defined in Section 7.4.9.

AEs will be coded using MedDRA. AEs will be summarized in various subsets, including on therapy AEs, related AEs, AEs leading to treatment discontinuation or withdrawal from study, SAEs, fatal AEs, etc. AEs will also be summarized by maximum intensity (mild, moderate, and severe).

Anti-albiglutide antibody results will be summarized by treatment group. In addition, the number and percentage of subjects with positive results along with the antibody titer values will be provided by visit.

The secondary endpoint FPG change from baseline at Week 26 will be analyzed analogous to the primary endpoint HbA1c using MMRM.

To assess the PD effect of albiglutide over time for the secondary endpoints change from baseline in HbA1c over time and change from baseline in FPG over time MMRM models will be used. The model will include HbA1c or FPG change from baseline at all post-baseline visits as dependent variables; treatment, visit week, and treatment-by-week interaction as fixed effects; baseline HbA1c or FPG as a continuous covariate; and subject as a random effect. Treatment effects estimates (and associated CI) of albiglutide liquid drug product will be evaluated within this MMRM model as least squares means contrasts relative to the lyophilized drug product. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion. In addition, PD effect of albiglutide over time for both HbA1c and FPG change from baseline over time will be evaluated in tabular and/or graphical format and summarized descriptively.

PK trough plasma concentration data will be summarized by treatment. No formal statistical analyses will be conducted.

9.4.3 Other Analyses

The analyses of the primary and secondary efficacy endpoints are described in Section 9.4.1 and Section 9.4.2. The details of any further planned analyses, including subgroup analysis and exploratory endpoints, will be provided in the RAP.

9.4.4 Supportive Analysis for Primary Endpoint: Exclusion of Data after Rescue

It is not expected to have a substantial number of subjects who will require rescue and that number of subjects would be similar for both treatment arms. However, to assess the impact of rescue, analysis of pre-rescue data will be performed. The model will be similar to the one used for the primary analysis. Results of this analysis will supplement the primary analysis. In addition, exclusion of data after treatment

discontinuation may also be performed if a significant number of subjects discontinue study medication prior to Week 26.

9.4.5 Missing Data

9.4.5.1 Impact of Missing Data on Primary Endpoint

Missing data, in the context of the primary analysis at Week 26, refer to those cases where the Week 26 HbA1c value is not available or was not collected. Missing data are not explicitly imputed in the primary MMRM analysis; although, there is an underlying assumption that data are missing at random. It is expected that the pattern of missing data will be similar in both treatment arms given that the treatment arms are the same drug but different formulas. All available scheduled post-baseline assessments up to endpoint are utilized and, via modeling of the within subject correlation structure, the derived treatment difference at Week 26 is adjusted to take into account missing data. The MMRM analysis (using saturated fixed effects and an unstructured variance-covariance matrix) is considered appropriate as the primary method of analysis, as it has been shown to give sensible answers to on-treatment questions in a range of practical situations [Siddiqui, 2009].

9.4.5.2 Extent of Missing Primary Analysis Data

Missing data is expected to arise mainly from subjects missing complete visits. The amount of missing data for those baseline covariates included in the statistical analysis is expected to be none or at worst minimal. If it should occur, that subject will effectively be lost to analysis. Missing data for HbA1c between two non-missing visits will be considered missing at random (intermediate missing data).

In this study, subjects who withdraw from treatment ***will be withdrawn*** from the study. In the eCRF, the reason for treatment discontinuation and the reason for withdrawal from the study are collected separately. Whenever the HbA1c value at Week 26 is missing (end of the study), the reason can be determined based on available data in these two locations.

The reason for missing data can be classified as follows: safety or procedural (including withdrawal of consent).

9.4.5.3 Reasons for Withdrawal

Reasons for withdrawal are assumed to fall into three broad categories:

- ***Procedural (e.g., lost to follow-up, withdrew consent, protocol deviation, study closed/terminated, and investigator discretion): In this case, it is expected that an assumption of missing at random (MAR) is appropriate for imputation of HbA1c data after withdrawal.***
- ***Safety (e.g., AE, subject reached protocol-defined stopping criteria): It is expected that, in most cases, any change in safety related to these reasons for withdrawal would have been captured prior to the subject withdrawing from***

the study. Missing HbA1c values after withdrawal due to safety concerns will be considered to possibly be missing not at random (MNAR).

Sensitivity analyses will be performed for data missing due to safety concerns.

9.4.5.4 Handling of Missing Data

The impact of missing data will be explored, as outlined below, for the ITT Analysis Population only.

Examination of Missing Data Patterns

It is expected that the pattern of missing data will be similar in both treatment arms given that each treatment arm is using the same drug but different formula.

To examine the nature of missing data, cohorts of subjects will be defined based on the scheduled assessments (HbA1c change from baseline) that were completed at Weeks 1, 4, 8, 12, 16, 20, and 26.

- Subjects who have week 1 assessment only
- Subjects who have assessments up to and including Week 4 only
- Subjects who have assessments up to and including Week 8 only
- Subjects who have assessments up to and including Week 12 only
- Subjects who have assessments up to and including Week 16 only
- Subjects who have assessments up to and including Week 20 only
- Subjects who have assessments up to and including Week 26.

The number and percentage of subjects on each treatment in the 7 cohorts defined here will be tabulated. Graphical methods will be used to examine changes from baseline over time to assess the pattern of outcomes prior to withdrawal.

Sensitivity Analyses – Multiple Imputation

Sensitivity analyses using multiple imputation methods will be conducted. Firstly, missing data between two non-missing time points will be considered missing at random.

The following multiple imputation methods are proposed based on whether data are missing at random or not missing at random:

- ***All missing data assumed MAR: Imputation is based on means and variances-covariances from subjects in the same treatment group as the withdrawn subject and is comparable to MMRM. The main differences are that this approach uses separate covariance parameter estimation for each arm, and also separate regression parameters are estimated on baseline covariates within each arm. This more complex parameterization of the imputation model compared with the analysis model is valid. This approach will be used for all data missing post***

withdrawal. Here the estimand is one where after withdrawal all subjects progress in a similar way to those who remain in the trial. We expect the MMRM and this to give similar inference. If so, then it indicates any difference between the primary MMRM analysis and multiple imputation sensitivity analysis is due to the assumed effect modification and the assumed rates of HbA1c increase after withdrawal, rather than anything to do with going from an MMRM approach to a multiple imputation approach.

- ***Missing due to the values of Week 26 HbA1c is not available or was not collected or due to safety concerns using last mean carried forward (LMCF) that is MNAR: This approach assumes that a constant rate of increase in HbA1c change from baseline is experienced by subjects following withdrawal from the study due to safety concerns. The MAR approach will be used for missing data due to procedural reasons. Sensitivity analyses using the LMCF approach will be performed using the following rates of HbA1c increase: 0%/month, 0.1%/month, and 0.2%/month to explore the potential impact as in a tipping-point analysis. For each treatment group, these 3 rates will be assumed, resulting in 9 scenarios. The resulting treatment differences and associated P-values for non-inferiority will be tabulated against the varying rates of HbA1c increase. This estimand is one where those who withdraw for safety concerns are assumed to revert to an unstable treatment regimen with an increasing rate of HbA1c.***

For each imputation data set, an analysis of variance will be carried using Week 26 data, both actual and imputed, using the same covariates as in the primary analysis. Contrasts of interest will be estimated and then combined across imputations using standard multiple imputation rules.

Additional scenarios for sensitivity analysis may be added and described in the RAP.

Amended text:

9.4 Key Elements of Analysis Plan

9.4.1 Primary Analyses

The primary endpoint is the change from baseline in HbA1c at Week 26. The primary analysis will include all HbA1c values collected at scheduled visits up to Week 26. This will include values after hyperglycemia rescue and discontinuation from investigational product. The primary analysis of the primary endpoint will be conducted using a mixed-effect model with repeated measures (MMRM) in the ITT Population. MMRM will use all available data. Imputation under the non-inferiority null hypothesis for missing data will be incorporated [Koch, 2008]. Multiple imputation will be used to replace missing data of change from baseline of HbA1c at Week 26 for all patients in both treatment arms as a first step, and then to make all the imputed values for the liquid drug product arm worse by the non-inferiority margin 0.4.

Multiple imputation approach uses separate covariance parameter estimation for each arm, and also separate regression parameters are estimated on baseline covariates within each arm. For subjects with missing data the imputation will use means and

variances-covariances from subjects in that treatment group where that subject with missing data belongs. This approach will be used for all data missing post withdrawal due to lost to follow-up or withdraws consent.

Non-inferiority testing will be performed at a one-sided alpha of 0.025 and non-inferiority margin of 0.4.

Further details of the imputation method for the primary analysis will be provided in the RAP.

The primary MMRM model will include HbA1c change from baseline at all post-baseline visits as dependent variables; treatment, region, age category, weight, background antidiabetic therapy, visit week, and treatment-by-week interaction as fixed effects; baseline HbA1c as a continuous covariate; and subject as a random effect. Treatment effects estimates (and associated CI) of albiglutide liquid drug product will be evaluated within this MMRM model as least squares means contrasts relative to the lyophilized drug product. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion.

9.4.2 Secondary Analyses

The evaluation of the safety and tolerability as assessed by immunogenicity and ISRs of albiglutide liquid drug product and the lyophilized drug product will be provided by reporting the event rates, and the associated 95% CI.

The overall general safety and tolerability of albiglutide liquid drug product versus lyophilized drug product will be evaluated in tabular and/or graphical format and summarized descriptively.

AEs and SAEs, physical examinations, clinical laboratory evaluations, vital sign measurements, and 12-lead electrocardiogram will be summarized by treatment group. For continuous variables, these summaries will include sample size, mean, median, standard deviation (and/or standard error), minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. The exposure-adjusted incidence rate will also be calculated as the number of events in a given period divided by the total person time on treatment of subjects at risk within the same period. The exposure-adjusted incidence rate will be expressed as an annualized rate expected. No inferential testing will be performed on the safety variables. Hypoglycemic events will be analyzed separately from other AEs. All hypoglycemic events will be classified as severe, documented symptomatic, asymptomatic, probable symptomatic, and pseudohypoglycemia, as defined in Section 7.4.9.

AEs will be coded using MedDRA. AEs will be summarized in various subsets, including on therapy AEs, related AEs, AEs leading to treatment discontinuation or withdrawal from study, SAEs, fatal AEs, etc. AEs will also be summarized by maximum intensity (mild, moderate, and severe).

Anti-albiglutide antibody results will be summarized by treatment group. In addition, the number and percentage of subjects with positive results along with the antibody titer values will be provided by visit.

The secondary endpoint FPG change from baseline at Week 26 will be analyzed using MMRM without imputation.

To assess the PD effect of albiglutide over time for the secondary endpoints change from baseline in HbA1c over time and change from baseline in FPG over time MMRM models will be used. The model will include HbA1c or FPG change from baseline at all post-baseline visits as dependent variables; treatment, visit week, and treatment-by-week interaction as fixed effects; baseline HbA1c or FPG as a continuous covariate; and subject as a random effect. Treatment effects estimates (and associated CI) of albiglutide liquid drug product will be evaluated within this MMRM model as least squares means contrasts relative to the lyophilized drug product. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion. In addition, PD effect of albiglutide over time for both HbA1c and FPG change from baseline over time will be evaluated in tabular and/or graphical format and summarized descriptively.

PK trough plasma concentration data will be summarized by treatment. No formal statistical analyses will be conducted.

9.4.3 Other Analyses

The analyses of the primary and secondary efficacy endpoints are described in Section 9.4.1 and Section 9.4.2. The details of any further planned analyses, including subgroup analysis and exploratory endpoints, will be provided in the RAP.

9.4.4 Supportive Analyses for Primary Endpoint

The primary endpoint change from baseline in HbA1c at Week 26 will be analyzed using the same MMRM model as described in Section 9.4.1 but missing data are not explicitly imputed in this supportive analysis; although, there is an underlying assumption that data is missing at random. All available scheduled post-baseline assessments up to endpoint are utilized and, via modeling of the within subject correlation structure, the derived treatment difference at Week 26 is adjusted to take into account missing data. The MMRM analysis (using saturated fixed effects and an unstructured variance-covariance matrix) is considered appropriate as the supportive analyses, as it has been shown to give sensible answers to on-treatment questions in a range of practical situations [Siddiqui, 2009].

Analysis excluding post-rescue and/or discontinuation from investigational product HbA1c data will also be performed as supportive. It is not expected to have a substantial number of subjects who will require rescue and that number of subjects would be similar for both treatment arms. However, to assess the impact of rescue, analysis of pre-rescue data will be performed. The MMRM model will be similar to the

one used for the primary analysis. Results of this analysis will supplement the primary analysis. No imputation will be conducted for this supportive analysis.

The primary endpoint HbA1c change from baseline at Week 26 may also be analyzed using MMRM model in the PP Population, if sample size is sufficient, imputation will not be conducted for this supportive analysis.

Further details of the supportive analyses will be provided in the RAP.

9.4.5 Missing Data

9.4.5.1 Impact of Missing Data on Primary Endpoint

Missing data, in the context of the primary analysis at Week 26, refer to those cases where the Week 26 HbA1c value is not available or was not collected or subject is lost to follow-up or withdraws consent. Missing data will be imputed in the primary MMRM analysis. To avoid bias in non-inferiority trials due to missing data, special attention will be paid to the handling of missing data in statistical analysis. Although, it is expected that the pattern of missing data will be similar in both treatment arms given that the treatment arms are the same drug but different formulations and it is expected that the impact of missing data on the primary endpoint to be minimal. Imputation under the non-inferiority null hypothesis [Koch, 2008] for all missing data for the primary analysis at Week 26 will be implemented.

9.4.5.2 Extent of Missing Primary Analysis Data

Missing data is expected to arise mainly from subjects missing complete visits. The amount of missing data for those baseline covariates included in the statistical analysis is expected to be none or at worst minimal. If it should occur, that subject will effectively be lost to analysis. Missing data for HbA1c between two non-missing visits will be considered missing at random (intermediate missing data).

In this study, subjects who withdraw from treatment ***will stay in the*** study. In the eCRF, the reason for treatment discontinuation and the reason for withdrawal from the study are collected separately. Whenever the HbA1c value at Week 26 is missing (end of the study), the reason can be determined based on available data in these two locations.

The reason for missing data can be classified as lost to follow-up or withdrawal of consent.

9.4.5.3 Reasons for Withdrawal

Reasons for withdrawal from the study are lost to follow-up or withdrawal consent. All subjects who discontinuation from investigational product due to the reasons listed under Section 5.5 will remain in the study and efficacy and safety data will be collected.

9.4.5.4 Handling of Missing Data

The impact of missing data will be explored, as outlined below, for the ITT Analysis Population only.

Examination of Missing Data Patterns

It is expected that the pattern of missing data will be similar in both treatment arms given that each treatment arm is using the same drug but different formula.

To examine the nature of missing data, due ***to lost to follow-up or withdrawal consent,*** cohorts of subjects will be defined based on the scheduled assessments (HbA1c change from baseline) that were completed at Weeks 1, 4, 8, 12, 16, 20, and 26.

- Subjects who have week 1 assessment only
- Subjects who have assessments up to and including Week 4 only
- Subjects who have assessments up to and including Week 8 only
- Subjects who have assessments up to and including Week 12 only
- Subjects who have assessments up to and including Week 16 only
- Subjects who have assessments up to and including Week 20 only
- Subjects who have assessments up to and including Week 26.

The number and percentage of subjects on each treatment in the 7 cohorts defined here will be tabulated. Graphical methods will be used to examine changes from baseline over time to assess the pattern of outcomes prior to withdrawal.

Sensitivity Analyses

The sensitivity of the results of analysis to the method of handling missing values will be investigated, especially if the number of missing values is substantial or if the characteristics of missing values differ between treatment groups.

To assess the impact of subjects who discontinued investigational product and stayed in the study; exclusion of data after treatment discontinuation may also be performed if a significant number of subjects discontinue study medication prior to Week 26. On treatment data will be analyzed using MMRM model as described in Section 9.4.1. Week 26 observations off-treatment will be imputed under the non-inferiority null hypothesis [Koch, 2008].

Sensitivity analyses using a different type of multiple imputation method will be conducted. Firstly, missing data between two non-missing time points will be considered missing at random (MAR). The analyses using the last mean carried forward (LMCF) approach will be performed using the following rates of HbA1c increase: 0%/month, 0.1%/month, and 0.2%/month to explore the potential impact as in a tipping-point analysis. For each treatment group, these 3 rates will be assumed, resulting in 9 scenarios. The resulting treatment differences and associated P-values for non-inferiority will be tabulated against the varying rates of HbA1c increase. This

estimand is one where those who withdraw are assumed to revert to an unstable treatment regimen with an increasing rate of HbA1c. For each imputation data set, an analysis of variance will be carried using Week 26 data, both actual and imputed, using the same covariates as in the primary analysis. Contrasts of interest will be estimated and then combined across imputations using standard multiple imputation rules.