TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	An Open-label Extension to Study 200952 to Evaluate the Long-term Safety, Tolerability and Pharmacodynamics of Albiglutide Liquid Drug Product in Subjects with Type 2 Diabetes Mellitus

Compound Number: GSK716155

Development Phase III/IV

Effective Date: 28-OCT-2015

Author(s): PPD

SPONSOR SIGNATORY:

PPD

10-28-2015

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Physician Project Leader

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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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

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

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1. PROTOCOL SYNOPSIS FOR STUDY 204682

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.

This open-label extension (Study 204682) to Study 200952 will provide additional safety, tolerability and immunogenicity data for the albiglutide liquid drug product.

Objective(s)/Endpoint(s)

Primary	
• **To provide extended safety, tolerability and immunogenicity data for the albiglutide liquid drug product.**	• Adverse events (AEs) and serious adverse events (SAEs), physical examinations, clinical laboratory evaluations, vital signs, and 12-lead electrocardiograms (ECGs). • Anti-albiglutide antibody production over time.
Exploratory	
• To provide safety and tolerability data on the transition from albiglutide lyophilized to liquid drug product. • To further evaluate the PD effect of albiglutide liquid drug product on HbA1c and FPG. • To gain additional patient experience with the albiglutide liquid drug product via auto-injector.	• AEs and SAEs, physical examinations, clinical laboratory evaluations, vital signs, and 12-lead ECGs. • Anti-albiglutide antibody production over time. • Change from baseline in HbA1c and FPG at Week 52. • Exploring patient experience and satisfaction.

Overall Design

- This is a 26 week, open-label, single group, multicenter, extension study to Study 200952. This extension study will provide extended safety, tolerability and immunogenicity data for the albiglutide liquid drug product.
- This extension study will recruit subjects who have completed Study 200952 and satisfy all inclusion/exclusion criteria.

- In addition to receiving albiglutide liquid drug product, subjects will continue on their current regimen of diet and exercise or stable dose of background metformin (if applicable).

Treatment Arms and Duration

- This extension study will comprise 2 study periods: treatment (26 weeks) and post-treatment follow-up (8 weeks).
- All subjects will receive 50 mg albiglutide liquid drug product via auto-injector.
- Study treatment will be administered once weekly by s.c. injection in the abdomen, thigh, or upper arm.

Type and Number of Subjects

- This extension study will recruit subjects who have completed Study 200952 and satisfy all inclusion/exclusion criteria.
- A maximum of 300 subjects will be eligible to take part in this extension study.

Analysis

Primary analyses:

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

The evaluation of the safety and tolerability as assessed by immunogenicity of albiglutide liquid drug product will be provided by reporting descriptive statistics.

Exploratory analyses:

The overall general safety and tolerability of albiglutide liquid drug product for subjects who are randomized to albiglutide lyophilized drug product in Study 200952 and transition to albiglutide liquid drug product in this extension study will be evaluated in tabular and/or graphical format and summarized descriptively.

The safety and tolerability as assessed by immunogenicity for the subject who transition to albiglutide liquid drug product in the extension study will be summarized descriptively.

HbA1c and FPG change from baseline will be summarized descriptively and/or graphically.

Patient experience and satisfaction with the auto-injector and albiglutide liquid product as measured by a self completed patient exit questionnaire at the end of treatment visit (Week 52) will be assessed using summary statistics.

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 and has been approved by the US FDA, the EMA and other regulatory agencies.

2.1. Study Rationale

Study 200952, a randomized, double-blind, repeat-dose study in subjects with T2DM will determine if there are any clinically relevant differences between albiglutide liquid drug product and albiglutide lyophilized drug product with respect to safety, tolerability and pharmacodynamic (PD) response. This open-label extension (Study 204682) to Study 200952 will provide additional safety, tolerability and immunogenicity data for the albiglutide liquid drug product.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• **To provide extended safety, tolerability and immunogenicity data for the albiglutide liquid drug product.**	• AEs and SAEs, physical examinations, clinical laboratory evaluations, vital signs, and 12-lead ECGs. • Anti-albiglutide antibody production over time.
Exploratory	
• To provide safety and tolerability data on the transition from albiglutide lyophilized to liquid drug product.	• AEs and SAEs, physical examinations, clinical laboratory evaluations, vital signs, and 12-lead ECGs.
• To further evaluate the PD effect of albiglutide liquid drug product on HbA_{1c} and FPG.	• Anti-albiglutide antibody production over time. • Change from baseline in HbA1c and FPG at Week 52.
• To gain additional patient experience with the albiglutide liquid drug product via auto-injector.	• Exploring patient experience and satisfaction.

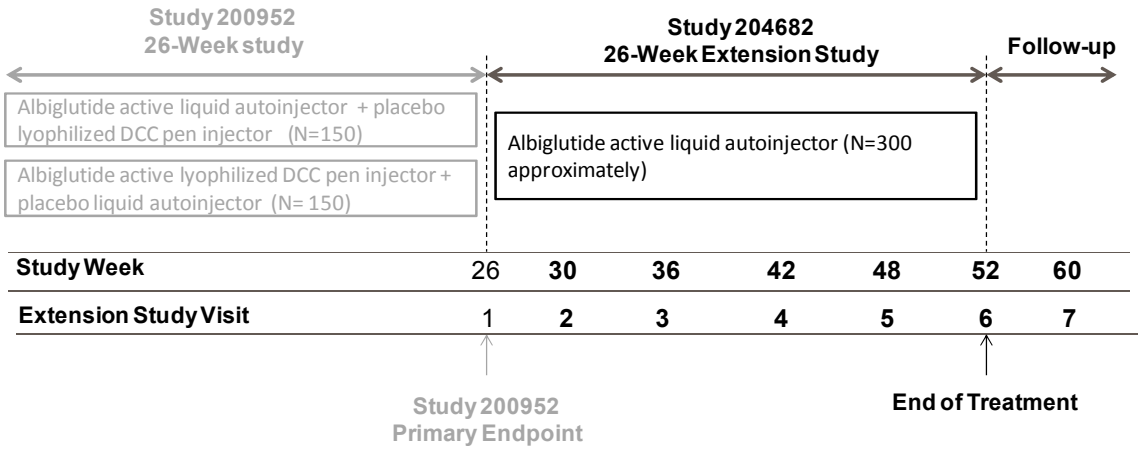
4. STUDY DESIGN

4.1. Overall Design

- This is a 26 week, open-label, single group, multicenter, extension study to Study 200952. This extension study will provide extended safety, tolerability and immunogenicity data for the albiglutide liquid drug product.

- This extension study will recruit subjects who have completed Study 200952 and satisfy all inclusion/exclusion criteria (Section 5).
- In addition to receiving albiglutide liquid drug product, subjects will continue on their current regimen of diet and exercise or stable dose of background metformin (if applicable).
- An overview of the study design is provided in Figure 1

Figure 1 Study Schematic



4.2. Treatment Arms and Duration

- This extension study will comprise 2 study periods (Figure 1): treatment (26 weeks) and post-treatment follow-up (8 weeks).
- All subjects will receive 50 mg albiglutide liquid drug product via auto-injector.
- Study treatment will be administered once weekly by s.c. injection in the abdomen, thigh, or upper arm.
- The first dose of study treatment will be administered by the subject during the clinic visit (Visit 1, Week 26) with supervision from clinic staff. All further doses of study treatment will be self-administered by the subject.
- 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

- This extension study will recruit subjects who have completed Study 200952 and satisfy all inclusion/exclusion criteria (Section 5).
- Maximum of 300 subjects will be eligible to take part in this extension study.

4.4. Design Justification

This is an open-label, long term extension to Study 200952. All subjects may choose to continue in the extension study if eligible to participate. The selected 26 week extension

treatment duration should appropriately capture the continuation of the safety, tolerability and immunogenicity data for the albiglutide liquid drug product.

4.5. Dose Justification

Phase III studies confirmed the glycemic efficacy of both 30 mg and 50 mg doses of albiglutide lyophilized drug 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 Investigator Brochure [IB] for further details).

In this extension study all subjects will receive 50 mg of albiglutide liquid drug product once weekly for 26 weeks.

4.6. Benefit:Risk Assessment

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.

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

A detailed description of the characteristics of the liquid drug product in the auto-injector device and results of nonclinical studies with this investigational formulation are presented in the IB Supplement.

Summary characteristics of the liquid drug product are shown in Table 1.

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

Component	Liquid Albiglutide	
	30 mg dose	50 mg dose
Injector type	***Pre-filled syringe with auto-injector***	
Final formulation pH	***5.9***	
Final albiglutide concentration	***50 mg/mL***	
Injection volume	***0.6 mL***	***1.0 mL***

Stability data thus far suggest that the same product-related variants/impurity profiles are present in the liquid and commercial lyophilized drug 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 pharmacokinetic (PK), PD, and clinical comparability between the liquid drug product and the lyophilized drug product is expected.

4.6.1. Risk Assessment

Key identified and potential risks associated with administration of albiglutide 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 drug product and the investigational liquid drug product. No risks specific to the liquid drug product have been identified in non-clinical studies to date. Mitigation strategies for this study have been incorporated for those risks (e.g., immunogenicity, injection site reactions) where a potential for differences between the liquid and lyophilized drug products has been recognized.

Please also refer to the IB and any 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 were excluded from entering study 200952. 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 5.4). 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 were excluded from entering study 200952. 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 were excluded from entering study 200952 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.	Subjects are neither allowed to use insulin nor insulin secretagogues during the study. Except as part of hyperglycemia rescue (see Section 5.3) 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	Hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III	Subjects with known allergy to any GLP-1 receptor agonist or excipients of albiglutide are excluded from entering

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
antidrug antibodies, severe hypersensitivity reactions, and other potential immune-related adverse events)	program with lyophilized albiglutide. Risk assessment of the albiglutide molecule predicted low immunogenic potential, which was substantiated for the commercial lyophilized 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 ISRs (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 drug product to form aggregates could have an impact on anti-drug antibody characteristics or immune related AE. However, the likelihood of clinically important changes in anti-drug antibody characteristics or immune related AEs with the albiglutide liquid drug product compared to the lyophilized product is considered low based on the absence of substantive qualitative differences between formulations.	study 200952 Subjects will be informed of the symptoms of severe hypersensitivity or allergy and be advised to seek medical assistance immediately. The development of anti-albiglutide antibodies and of injection site reactions 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 formulation, 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 anti-drug antibody positive subjects reported one or more injection site reactions) than among those who were consistently antibody negative (14% of the antidrug antibody negative	Subjects 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	subjects reported one or more injection site reactions). Overall, for lyophilized albiglutide, ISRs 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 drug product) may impact the injection site reaction profile.	
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) were excluded from entering study 200952. Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.
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) were excluded from entering study 200952. 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 5.4).
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	Subjects with a history of cancer were excluded from enetering. study 200952 Risk communication via guidance for investigators (see

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	biological plausibility [European Public Assessment Report, 2014], and hematological malignancies [FDA Summary Basis of Approval, 2014].	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+ 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 were excluded from entering study 200952 . 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 5.4.1).
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	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 . 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
	compared to those with mild renal impairment. GI events may lead to dehydration and worsen renal function.	
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 were excluded from Study 200952.

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 currently no data available for the use of the albiglutide liquid drug product in humans. 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 drug product and lyophilized drug product 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 that have been 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 GlaxoSmithKline (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 albiglutide 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 extension study only if all of the following criteria apply:

[1] TYPE OF SUBJECT
1. Subjects who have completed the 26 week Treatment Phase of Study 200952

[2] SEX
2. Male or female 3. 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.

[3] INFORMED CONSENT
4. 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] TYPE OF SUBJECT
1. Subject meets one or more of the withdrawal stopping criteria at Visit 1 (Week 26) (see Section 5.4)

5.3. Hyperglycemia Rescue

During the study of diabetics, there is always the possibility of hyperglycemia which might impact subject safety. 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
≥Week 26 and <Week 52	HbA_{1c} ≥8.5%

1. HbA_{1c} = glycosylated hemoglobin

Subjects can be rescued at any time. Subjects who qualify for rescue should return to the study center for a rescue visit, which includes efficacy assessments. The laboratory assessments should include safety laboratory tests (e.g., chemistry and complete blood count) and HbA_{1c}. 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 and uptitration 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 study medication and appropriate rescue therapy initiated. Such subjects will continue to be followed in the study for their cardiovascular and other safety information; however, they will not receive further 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.

5.4. 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 5.4.1
  - QTc abnormalities exceeding the threshold criteria outlined in Section 5.4.2.
  - 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 discontinue active participation in the study will no longer receive 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.

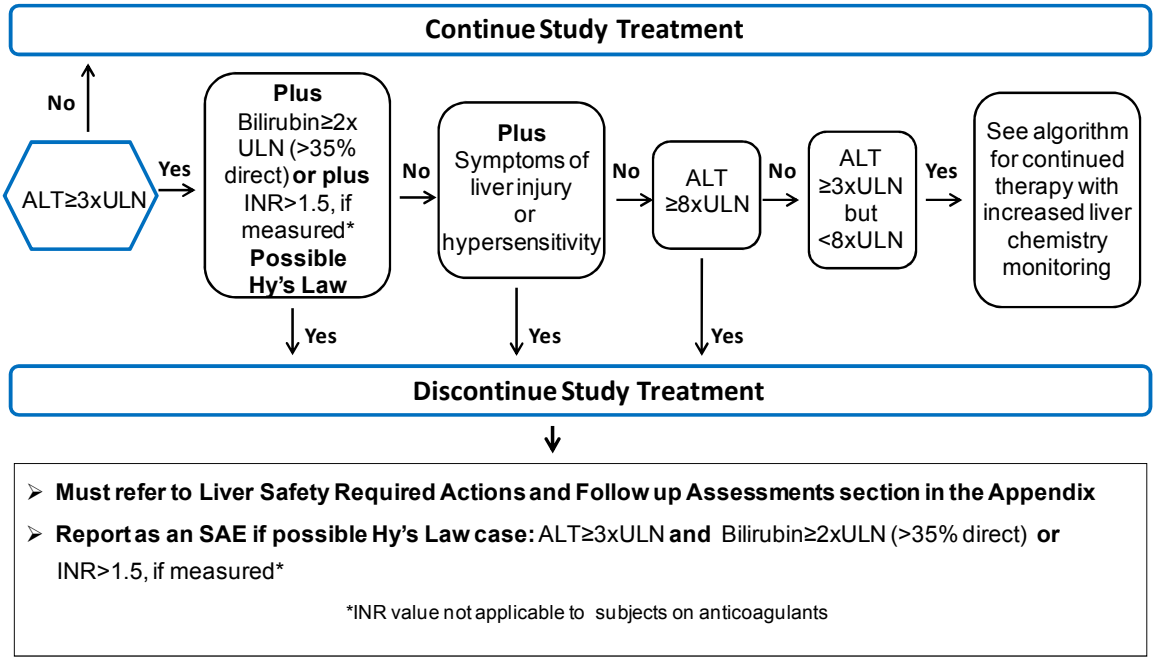
Withdrawn subjects will not be replaced.

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.

5.4.1. Liver Chemistry Stopping Criteria

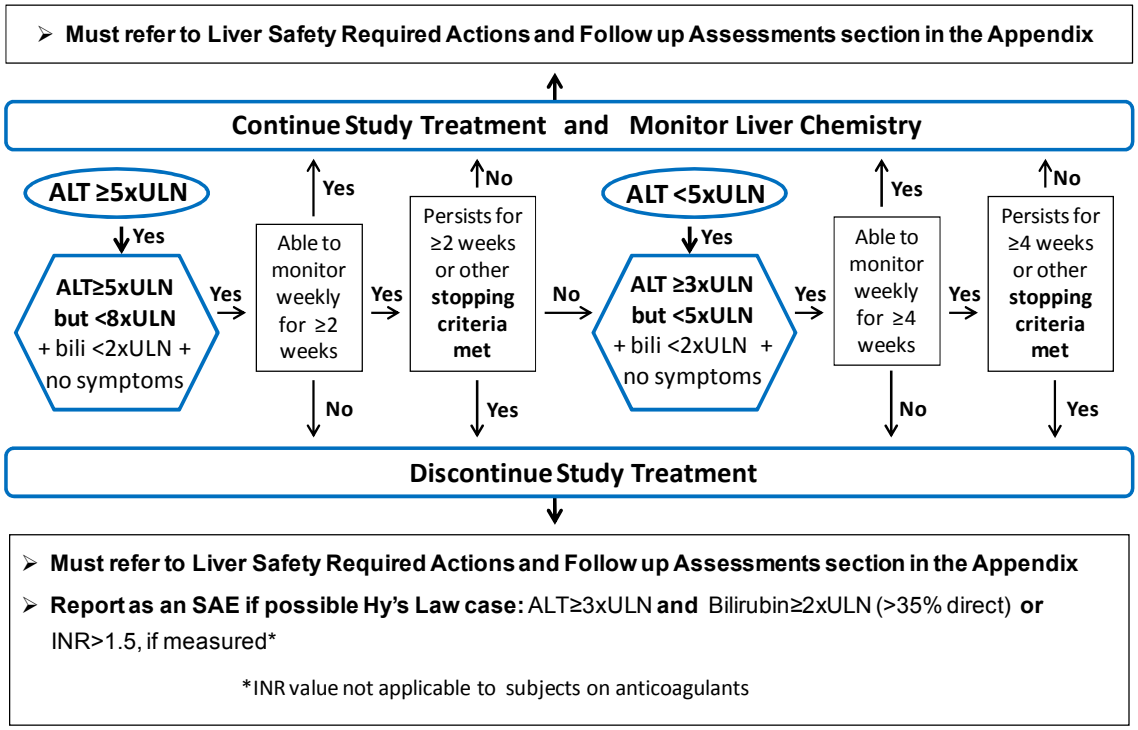
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV Liver Chemistry Stopping 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 ≥3x upper limit of normal (ULN) but <8xULN



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

5.4.1.1. 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.

5.4.2. 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 be withdrawn from the study:

- QTcF > 500 msec (or ≥530 ms for subjects with bundle-branch block or pacemaker)

5.5. Subject and Study Completion

A completed subject is one who has completed the 26 week treatment phase of the extension 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:	Albiglutide liquid auto-injector
Dosage form/Delivery system:	Albiglutide liquid drug product is provided as a fixed-dose, disposable auto-injector containing albiglutide liquid drug product (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 drug product. Albiglutide liquid drug product (50mg) has a pH of 5.9. The auto-injector delivers the study treatment in an injection volume of 1.0 mL for the 50 mg dose.
Unit dose strength(s) /Dosage level(s):	50mg albiglutide
Route of Administration	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 at any time of day without regard to meals

6.2. Treatment Assignment

All subjects will receive 50 mg albiglutide liquid drug product via auto-injector.

6.3. Planned Dose Adjustments

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

Subjects on a stable dose of metformin at the start of study 200952 may have their metformin dose adjusted during the extension study at the discretion of the investigator based on clinical need.

6.4. Blinding

This extension study will be an open-label study.

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 subject or designee will administer study treatment at the time points specified in the Time and Events Table (Section 7.1).

Subjects will be instructed to return all unused and used auto-injectors at the visits specified in the Time and Events Table (Section 7.1) in order to perform drug accountability and determine compliance. In addition, subjects will be provided with a pre-printed card at each dispensing visit to record the date of each dose. The card is to be returned at the next dispensing visit.

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 four weeks for 12 weeks. This dose was associated with an increased frequency of nausea, vomiting, and headache.

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

6.9. Treatment after the End of the Study

Following completion of the Week 52 visit, subjects will return to the study centre in 8 weeks for the post-treatment follow-up visit (Week 60 visit) and will complete the study.

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 Visit 1 (Week 26) 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 drug product taken as study treatment) are prohibited.
- Any investigational drug other than study treatment (albiglutide liquid drug product).
- 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.

7.1. Time and Events Table

Procedure		Treatment					[11]End of Treatment	Follow-up[12]
	Extension Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
	Study Week	**26[13]**	**30**	**36**	**42**	**48**	**52**	**60**
Informed consent for Study 204682		X						
Inclusion/exclusion criteria review[1]		X						
Full (F) or brief (B) physical exam[2]		F	B	B	B	B	F	F
Weight		X	X	X	X	X	X	X
12-lead ECG[3]		X					X	X
Vital signs		X	X	X	X	X	X	X
Serum (S)/Urine (U) pregnancy test (WCBP)		S	U	U	U	U	S	
Clinical chemistry/hematology samples[4]		X	X	X		X	X	X
Lipids (including total cholesterol, LDL-C, HDL C, triglycerides, FFAs)[4]		X					X	X
Urinalysis[5]		X					X	
HbA_{1c} [6,7]		X	X	X	X	X	X	X
FPG [7]		X	X	X	X	X	X	X
eGFR		X		X		X		
Immunogenicity sample[8]		X	X	X			X	X
Review AE/SAE, concomitant medication and hypoglycemia events		X	X	X	X	X	X	X
Advice on diet and exercise[9]		X	X	X	X	X	X	
Subject Experience / Satisfaction Exit Questionairre							X	
Study treatment dispensed		X	X	X	X	X		
Study treatment compliance[10]			X	X	X	X	X	

WCBP: Women of child bearing potential; FFA: free fatty acids; LDL-c: low density lipoproteins cholesterol; HDL-c: high density lipoproteins cholesterol

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 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 7.3.3.
3. 12-lead ECGs will be obtained **before** measurement of vital signs and collection of blood samples for laboratory testing. See Section 7.3.5.
4. Clinical chemistry and hematology assessments are described in Section 7.3.6.

5. Urine samples should be collected in the early morning.
6. Blood samples for HbA_{1c} should be collected before administration of study treatment.
7. Subjects will have their FPG and HbA_{1c} levels evaluated to monitor for potential hyperglycemia.
8. Blood samples for immunogenicity are to be collected **before** study drug administration.
9. Standard diabetic dietary and exercise advice will be reinforced through the end-of-treatment visit.
10. Compliance will be assessed as described in Section 6.7.
11. Subjects who discontinue study treatment should be handled as described in Section 5.4.
12. Follow-up visit for subjects who have discontinued study treatment (see Section 5.4) or subjects who have completed the 52 week treatment period.
13. Visit 1 of 204682 is also the end of treatment visit in Study 200952.
14. Visit 1 of Study 204682; albiglutide liquid drug product administered to all study subjects.

7.2. Screening and Critical Baseline Assessments

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

Full details of assessments undertaken at Visit 1 (Week 26) are provided in the Time and Events Table Section 7.1.

7.3. 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.

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

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

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

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

- 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.
- AEs will be collected from the start of study treatment until the follow-up contact (see Section 7.3.1.3), 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.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- 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 4.

7.3.1.2. 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?"

7.3.1.3. 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 7.3.1.5) 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 5.4). Further information on follow-up procedures is given in Appendix 4.

7.3.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 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 Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF 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.

7.3.1.5. 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 7.3.1.4)

- 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 be withdrawn from the study and should not be rechallenged with albiglutide (see Section 5.4 for complete list of AEs of special interest requiring withdrawal).

7.3.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs 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.

7.3.2. 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 5.

7.3.3. 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

Weight will be measured at each clinic visit.

7.3.4. 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.

7.3.5. Electrocardiogram (ECG)

A single 12-lead ECG recording (with subject in semi-recumbent 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 5.4.2 for QTc withdrawal criteria.

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

7.3.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 4 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. The results of the test must be entered into the eCRF.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 4.

Table 4 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet Count; RBC Count; Hemoglobin; Hematocrit *RBC Indices*: mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH) *WBC count with Differential:* Neutrophils; Lymphocytes; Monocytes; Eosinophils; Basophils
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 • Lipids including total cholesterol, LDL-C, HDL C, triglycerides, FFAs (fasting) [2] • FSH and estradiol (as needed in women of non-child bearing potential only) • 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 5.4.1 and Appendix 3.
2. Fasting is defined as no food or drink (except water) for at least 8 hours before blood draw

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.

7.3.7. Estimated Glomerular Filtration Rate (eGFR)

Serum creatinine will be measured at the timepoints 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).

7.3.8. 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 1 (Week 26) and reinforced at each study site visit through the End of treatment visit (Week 52). 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.

7.3.9. 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 4) 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.

7.4. Tracking of Albiglutide Liquid Auto-injector Failures and User Errors

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

NOTE: Albiglutide 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 7.3.1.

7.5. Immunogenicity

Serum for antidrug antibody testing will be obtained from all subjects before administration of study treatment according to the Time and Events Table in Section 7.1. With exception of Week 30, all other time points (Week 26, Week 36, Week 52 and Week 60 (Follow-up)) are comparable to those collected in the Phase III Harmony studies with lyophilized albiglutide and may serve as comparators to the formulation of the marketed product.

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 6).

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 as per the Protocol Time and Events Schedule in Section 7.1.

7.6. 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.

7.7. Value Evidence and Outcomes

In this open-label extension study, subjects will self-administer their medication via the auto-injector device, thereby gaining first time personal experience with its use. Subject experience with the auto-injector device and treatment will be collected via a patient self-completed exit questionnaire at the end of treatment visit (Week 52). The close-ended questionnaire focuses on elements of burden, experience and satisfaction with the auto-injector and albiglutide liquid drug product. Specifically, the questions evaluate how comfortable subjects feel about using the device, how long it took for them to feel comfortable using the device, how easy they think it is to use, how long it takes to prepare/administer and whether they prefer it to other methods for self-injection (assuming that they have prior experience) (see Appendix 8 for further details)

7.8. Genetics

Information regarding genetic research is included in Appendix 7

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

This open label study is designed to evaluate the extended safety and tolerability as assessed by immunogenicity of albiglutide liquid drug product when used in subjects with T2DM for additional 26 weeks. The overall general safety and tolerability of albiglutide liquid drug product will be assessed by reporting descriptive statistics.

9.2. Sample Size Considerations

The total number of subjects for this study will be determined by the number of subjects who give consents to enroll in this study from the parent Study 200952, have completed Study 200952, and satisfy all inclusion/exclusion criteria. Therefore, it is anticipated to enroll a maximum of 300 eligible subjects who will receive albiglutide liquid drug product.

9.2.1. Sample Size Assumptions

No sample size assumptions are planned for this study.

9.2.2. Sample Size Sensitivity

No sample size sensitivity is planned for this study.

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

Safety Population: The Safety Population is defined as all enrolled subjects who receive at least 1 dose of study medication.

Intent-to-Treat (ITT) Population: The ITT Population will include all subjects who receive at least 1 dose of the study medication and have a baseline assessment.

Other analysis populations may 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 overall general safety and tolerability of albiglutide liquid 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. 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 7.3.9.

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).

The evaluation of the safety and tolerability as assessed by immunogenicity of albiglutide liquid drug product will be provided by reporting descriptive statistics.

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

Summary data for the primary analyses will be presented by visit and by subjects who needed hyperglycemic rescue during Study 200952 (at visit 1 of the current study), by subjects who did not need hyperglycaemic rescue during study 200952, and overall.

9.4.2. Exploratory Analyses

The overall general safety and tolerability of albiglutide liquid drug product as assessed by AEs and SAEs, physical examinations, clinical laboratory evaluations, vital sign measurements, and 12-lead ECGs for subjects who are randomized to albiglutide lyophilized in Study 200952 and transition to albiglutide liquid drug product in this extension study will be summarized analogous to the data in Section 9.4.1.

The safety and tolerability as assessed by immunogenicity for the subjects who transition to albiglutide liquid drug product in this extension study will be summarized descriptively.

The exploratory endpoints change from baseline for HbA_{1c} and FPG at week 52 for those subjects who transition to albiglutide liquid product will be presented in tabular and/or graphical format and summarized descriptively together with the 95% CI.

Patient experience and satisfaction will be assessed using descriptive summary statistics of individual questions of the 9-item questionnaire (Appendix 8).

Summary data for the exploratory analyses will be presented by subjects who needed hyperglycemic rescue during Study 200952 (at Visit 1 of the current study), by subjects who did not need hyperglycaemic rescue during study 200952, and overall.

9.4.3. Other Analyses

No other analyses will be conducted for this study.

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 favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

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

The study will also be conducted in accordance with ICH 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

- 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 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.

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

Egan AG, Blind E, Dunder K, de Graeff PA, Hummer BT. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. N Engl J Med. 2014; 370(9):794-7.

European Public Assessment Report (EPAR) for Eperzan. 2014. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002735/human_med_001735.jsp&mid=WC0b01ac058001d124

FDA Summary Basis of Approval. 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125431Orig1s000TOC.cfm

Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150: 604-12.

Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013; 36:1384-95.

12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BUN	blood urea nitrogen
CI	confidence interval
CPK	creatine phosphokinase
CV	cardiovascular
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
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GSK	GlaxoSmithKline
HA	human albumin
HbA1c	glycated hemoglobin
hCG	human chorionic gonadotrophin
HDL-c	high density lipoproteins
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
LDH	lactate dehydrogenase
LDL-c	low density lipoproteins;

MACE	major adverse cardiovascular event
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
MSDS	Material Safety Data Sheet
MTC	medullary thyroid cancer
PAC	Pancreatitis Adjudication Committee
PD	pharmacodynamics
PK	pharmacokinetics
OC RDC	Oracle Clinical Remote Data Capture
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
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
SpectrMAX

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

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

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>International Normal Range (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)
• Do not restart/rechallenge subject with</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 deoxyribonucleic acid (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).
• Fractionate bilirubin, if total</td></tr>
</table>

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	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 adduct 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.