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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number : 2015N255772_01

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

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

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

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1. PROTOCOL SYNOPSIS FOR STUDY 204879

Rationale

To gain insight into a potential peripheral mechanism of nausea associated with glucagon-like peptide-1 receptor (GLP-1R) agonists; this study will compare the effect of albiglutide and exenatide on gastric myoelectrical activity (GMA), gastric emptying (GE) and nausea [as measured by visual analogue scale (VAS)] in subjects with type 2 diabetes mellitus (T2DM). The study is divided in two parts. Part A will characterize the GMA, GE and nausea response to exenatide and confirm exenatide as a positive control for Part B. Part B will compare the effects of albiglutide and exenatide on GMA, GE and nausea.

Objective(s)/Endpoint(s)

Part A is a pilot phase. Part B primary and secondary objectives are listed below:

Part B Objectives

Objectives	Endpoints
Primary	
To evaluate the effect of albiglutide compared to exenatide on GMA.	<ul style="list-style-type: none"> Change from baseline in electrogastragram (EGG) parameters at Weeks 2, 5, and 8 at each time interval (pre-and 10, 20 and 30 min after water load). <ul style="list-style-type: none"> Distribution of average power by frequency region (as % of power). Ratios of average power post-water load test (post-WLT)/pre water load test (pre-WLT) by frequency region. Percentage (%) of time with the dominant EGG frequencies in the four frequency ranges (bradygastria, normal, tachygastria and duodenal). Change from baseline in EGG parameters related to VAS of nausea at Week 2, 5, and 8 at each time interval (pre-and 10, 20 and 30 min after water load)
Secondary	
To assess the effect of albiglutide on GE compared to exenatide	<ul style="list-style-type: none"> Change from baseline of time to half gastric emptying (GE_{t1/2}) at Week 5 and 8 Change from baseline of profiles of ¹³C excreted in breath (kPCD¹) at Weeks 5 and 8 at each time interval (45, 90, 120, 150, 180 and 240 min)

Objectives	Endpoints
To assess the effect of albiglutide on the volume of water ingested during EGG compared to exenatide	<ul style="list-style-type: none"> Change from baseline of volume of water ingested during water load EGG test at Weeks 2, 5 and 8.
To evaluate the effect of albiglutide on stomach fullness, hunger, bloating and abdominal pain during EGG with water load test compared with exenatide	Change from baseline of VAS of stomach fullness, hunger, bloating and abdominal pain during the EGG water load test at each time interval (pre-and 10, 20 and 30 min after water load) at Week 2, 5, and 8.
To evaluate safety and tolerability of albiglutide and exenatide	<ul style="list-style-type: none"> Vital signs, clinical laboratory tests, adverse events (AEs), and Gastroparesis Cardinal Symptom Index – Daily Diary (GCSI-DD). Nausea AEs presenting outside the timing of the WLT and GCSI-DD.
Exploratory	
To evaluate change in gastric rhythm status (Data permitting)	<ul style="list-style-type: none"> At Weeks 2, 5, and 8; over 30 min and at each time interval (pre-and 10, 20 and 30 min after water load). <ul style="list-style-type: none"> Number and % of subjects with a shift in gastric rhythm status. Number and % of subjects by gastric rhythm status. Mean and mean change from baseline in average dominant frequency

1. Percent dose excreted of ^{13}C *1000

Overall Design

Part A Overall Design

- Part A is a single arm, open label pilot phase to evaluate the effect of 5-day repeated doses of exenatide (10 µg twice daily) on GMA, GE and nausea in subjects with T2DM.
- Part A will comprise 3 study periods: screening/wash-out (up to 3 weeks), treatment (5±1 days), and post-treatment follow-up (within 7 days after the last dose of exenatide).
- Part A will recruit subjects with T2DM (>6 months since diagnosis) with glycated hemoglobin (HbA_{1c}) >6.5% and ≤9.0%, fasting plasma glucose (FPG) ≤210 mg/dL (central lab) at screening and on a current regimen of diet and exercise or a stable dose of one oral anti-diabetic medication (OAM) (maintained for ≥ 2 months prior to screening).
- Fasting capillary blood glucose will be confirmed to be ≤230 mg/dL at baseline.
- Subjects receiving monotherapy with an OAM of metformin, sulfonylurea, sodium-glucose co-transporter-2 (SGLT2) inhibitors, or meglitinide at screening will be

washed out for 2 days for immediate release and 4 days for extended release OAM prior to baseline.

- A subject's nutritional plan will be optimized prior to baseline and maintained during the entire study.
- All evaluations and assessments will be performed as outpatient visits.
- Subjects will undergo 2 EGG and 2 gastric emptying breath tests (GEBT) assessments.
- At the end of the Part A, subjects previously on an OAM will restart OAM at the discretion of the investigator after the last dose of exenatide. The half-life of exenatide (2-3 hours) should be taken into consideration.

Part A - Treatment Arms and Duration

Part A is a single arm. All subjects will receive 10 µg subcutaneous exenatide twice daily for 5±1 days. The total duration of a subject's participation will be approximately 5 weeks.

Part A – Type and Number of Subjects

- A sufficient number of subjects with T2DM will be screened and enrolled to achieve approximately 10 evaluable subjects.
- If subjects prematurely discontinue the Part A, additional replacement subjects may be enrolled at the discretion of the Investigator in consultation with the Sponsor.

Part A Data Review

Once Part A is complete, data will be reviewed and a decision to progress or not to Part B will be made. A decision to progress to Part B will be made based on the confirmation that change in GMA caused by the administration of exenatide is detectable by an EGG with WLT. Confirmation of safety when adding the WTL on top of a GLP1 receptor agonist will be required to progress to Part B. Adjustments to the study design of Part B (e.g., endpoint evaluation and/or number of subjects) may be made prior to progression to Part B. Details will be described in the Reporting and Analysis Plan (RAP).

Part B: Overall Design

- Part B is randomized, open-label, multicenter, active-controlled, parallel-group study of 8 weeks treatment duration to compare the effects of albiglutide on GMA, GE and nausea as measured by VAS with exenatide as a positive control. The central readers of EGG and GEBT tests will be blinded to assigned treatments.
- Part B will comprise 3 study periods: screening/wash-out (up to 3 weeks), treatment (8 weeks), and post-treatment follow-up (4 weeks).
- Part B will recruit subjects with T2DM (>6 months since diagnosis) with HbA_{1c} >6.5% and ≤9.0%, FPG ≤210 mg/dL (central lab) at screening and on a current regimen of diet and exercise or a stable dose of one OAM (maintained for ≥ 2 months prior to screening).

- Fasting capillary blood glucose will be confirmed to be ≤ 230 mg/dL at baseline.
- Subjects participating in Part A are not allowed to participate in Part B.
- Subjects receiving monotherapy with an OAM of metformin, sulfonylurea, SGLT2-inhibitor, or meglitinide will be washed out for 2 days for immediate release and 4 days for extended release OAM prior to randomization.
- A subject's nutritional plan will be optimized prior to randomization and maintained during the entire study.
- All evaluations and assessments will be performed as outpatient visits.
- Subjects will undergo 4 EGG and 3 GEBT assessments.
- At the end of the Part B subjects previously on an OAM will restart OAM at the discretion of the investigator after the last dose of study treatment. The half-life of albiglutide/exenatide should be taken into consideration.
- At randomization, subjects will be stratified by screening HbA_{1c} value ($<7.5\%$ and $\geq 7.5\%$), and background use of OAM (OAM use versus no OAM use). Additional stratification may be added based on the results from Part A.

Treatment Arms and Duration

- Subjects will be randomized in a 1:1 ratio to either albiglutide or exenatide.

Medication	Albiglutide Group	Exenatide Group
Albiglutide or Exenatide	After Baseline EGG on Day 1: once weekly SC injection at 30 mg for 4 weeks.	After Baseline EGG on Day 1: twice daily SC injection at 5 µg for 4 weeks.
	From Week 5 Day 1: uptitrate to 50 mg once weekly SC injection for 4 weeks	From Week 5 Day 1: uptitrate to 10 µg twice daily SC injection for 4 weeks

SC = subcutaneous

- Total duration of a subject's participation will be approximately 15 weeks.
- Down-titration (dose reduction) of albiglutide or exenatide is **NOT** permitted. If a subject experiences tolerability issues then the subject may be withdrawn from the study at the discretion of the investigator.

Type and Number of Subjects

- Approximately 62 subjects with T2DM will be randomized. Assuming 20% of subjects will be withdrawn or lost to follow-up this will allow for 50 evaluable subjects (25 evaluable subjects per treatment group).

Analysis

The primary and secondary endpoints will be analyzed using a mixed-effect model with repeated measures (MMRM). The MMRM will be assessed to compare albiglutide to exenatide.

2. INTRODUCTION

2.1. Study Rationale

GLP-1R agonists (i.e., exenatide, liraglutide, albiglutide, lixisenatide, and dulaglutide) are medications for the treatment of T2DM. All have demonstrated reductions in HbA_{1c}, FPG without body weight gain while having a low risk of hypoglycemia.

Gastrointestinal (GI) adverse events are relevant for this therapeutic class, with increased incidence of nausea and vomiting [Leiter, 2014; Reusch, 2014; Rosenstock, 2009; Neumiller, 2009]. Various mechanisms have been proposed to explain the pathophysiology of nausea associated with GLP-1R agonists, including food accumulation in the stomach due to slowing gastric emptying, activation of peripheral GLP-1R and subsequent stimulation of the central nervous system (CNS) via vagal afferents and direct activation of CNS GLP-1R [Baggio, 2004]. The incidence of nausea varies among the members of this therapeutic class [Sun, 2012, Trujillo, 2015].

The dose- and time-dependent effects of albiglutide were evaluated in a Phase 2b dose ranging, open-label, active reference (exenatide) study. The proportion of subjects with nausea and or vomiting was less than 10% at each week with albiglutide 30 mg weekly and declined over time, with no nausea or vomiting after 8 weeks. The incidence of nausea and/or vomiting with exenatide reached 20% by week 2, increased at week 5 to a peak incidence of 29% after uptitration and declined over time [Rosenstock, 2009]. Albiglutide 50 mg weekly dose was not included in this study. However 50 mg bi-weekly and monthly and 100 mg monthly were studied. Starting albiglutide at 50- or 100 mg was associated with a higher incidence of nausea/vomiting.

In a head to head, 32-week, open-label clinical trial in patients with T2DM, in which non-inferiority of albiglutide of a 95% confidence interval (CI) upper margin of 0-3% for HbA_{1c} was not met, the incidence of nausea was 9.9% for albiglutide and 29.2% for liraglutide, and the incidence of vomiting 5.0% and 29.3% respectively [Pratley, 2014]. In a 26-week open-label, forced titration clinical trial, nausea was reported in approximately 25.5% and 28% of subjects treated with liraglutide and exenatide, respectively [Buse, 2009]. In exenatide Phase 3 program, nausea was reported in up to 44% of subjects receiving exenatide [Byetta, US Prescribing Information, 2015]. Dulaglutide, another once weekly GLP-1R agonist reported ~20% incidence of nausea at the highest approved dose in the results from pooled placebo-controlled trials [Trulicity, US Prescribing Information, 2015].

The reasons for the differences in incidence of nausea in clinical trials between albiglutide and other GLP-1R agonists are not fully understood. Potential explanations include differences in the pharmacokinetic profiles (e.g., albiglutide T_{max} ~3 days, dulaglutide T_{max} ~2 days, exenatide T_{max} ~2.1 h, or liraglutide T_{max} ~13h). It is unknown if these differences result in compound specific patterns of receptor occupancy and pharmacodynamic response. Differences in molecular size and structure among GLP-1R agonists may also impact penetration through the blood brain barrier and activity in brain receptors.

Electrogastrogram (EGG) is a noninvasive technique to assess GMA [Koch, 2001]. It is used in clinical practice to identify if patients with nausea and other upper GI symptoms without mechanical causes have disturbances in the myoelectrical gastric rhythm, and to confirm the diagnosis of gastroparesis. “EGG with water load test” is a standardized test to induce gastric distention and measure myoelectrical responses as well as collect VAS of upper gastrointestinal symptoms (stomach fullness, hunger, nausea, bloating and abdominal pain) under standardized conditions. The gastric distention produced by the water load induces nausea in a high proportion of patients, allowing the assessment of GMA during the episodes of nausea. Episodes of nausea are typically associated with disturbance in GMA called gastric dysrhythmias.

To gain insight into a potential peripheral mechanism of nausea associated with GLP-1R agonists; this study will compare the effect of albiglutide and exenatide on GMA, GE and VAS of nausea in T2DM subjects. Albiglutide will be administered weekly at the initial dose of 30 mg and uptitrated to 50 mg after 4 weeks. Exenatide will be administered twice daily at dose of 5 µg and uptitrated to 10 µg twice daily after 4 weeks. The study is divided in two parts. Part A will characterize the GMA, GE response and nausea to exenatide and confirm exenatide as a positive control for Part B. Part B will compare the effects of albiglutide and exenatide on GMA, GE and nausea.

2.2. Brief Background

Albiglutide is a recombinant fusion protein (molecular weight of ~73kDa) consisting of two copies of a 30-amino-acid sequence of modified human GLP-1 linked in tandem to human albumin [Matthews, 2008; Bush, 2009]. The GLP-1 sequence has been modified to confer resistance to DPP-4-mediated proteolysis. These modifications greatly extend the half-life (approximately 5 days), allowing once weekly dosing by subcutaneous injection and a steady state within 3-4 weeks. The efficacy and safety of albiglutide has undergone extensive testing both as monotherapy and in combination with oral anti-diabetic agents [Home, 2015; Ahren, 2014; Weissman, 2014; Rosenstock, 2014; Leiter, 2014; Nauck, 2015]. Reductions in HbA_{1c} are typically 0.3-1.0% with 30-mg uptitrated to 50-mg. In clinical trials, albiglutide demonstrated a GI side-effect profile similar to placebo [Ahren, 2014].

Exenatide is a 39 amino acid peptide that shares 53% sequence homology with human GLP-1 [Goke, 1993]. Due to its short half-life, exenatide is administered twice daily. The incidence of GI effects was reported most frequently at initiation of therapy (0-8 weeks) and decreased over time, i.e., nausea may resolve within 6-8 weeks in most patients [Heine, 2005; Meretto, 2008; Buse, 2004; DeFronzo, 2005; Kendall, 2005; Zinman, 2007; Nauck, 2007; Barnett, 2007].

In normal subjects the GMA is generated by the pacemaker interstitial cells of Cajal, located in upper third of gastric body on the greater curvature, that discharge at a normal frequency of 3 cycles per minute (cpm) [Koh, 1998]. The shift of frequency from normal GMA to a slower (bradygastria) or faster (tachygastria) rhythm is termed as gastric dysrhythmia. These gastric dysrhythmias have been linked to nausea in clinical trials, and the use of GMA assessed in EGG with water load test has been suggested as a useful tool to evaluate and characterize nausea in a variety of clinical conditions [Koch, 2001].

A preclinical study in ferrets demonstrated that exenatide administered peripherally induced retching and resulted in gastric dysrhythmias detected using radiotelemetry [Lu, 2014]. No studies to date have evaluated the effect of GLP-1R agonists on GMA in humans.

GEBT is a recently FDA approved method to measure GE of solid food in adults. Performance characteristics of GEBT are comparable to those of the gold standard of gastric emptying scintigraphy. GEBT is a non-radioactive and non-invasive technology.

3. OBJECTIVE(S) AND ENDPOINT(S)

3.1. Part A: Objectives and Endpoints

Objectives	Endpoints
Exploratory	
To evaluate the effect of exenatide on GMA	<ul style="list-style-type: none"> Change from baseline of EGG parameters at each recording time interval (pre-and 10, 20 and 30 min after water load) compared to baseline: <ul style="list-style-type: none"> Distribution of average power by frequency region (as % of power) Ratios of average power post- WLT/pre- WLT by frequency region Percentage (%) of time with the dominant EGG frequencies in the four frequency ranges (bradygastria, normal, tachygastria and duodenal) Change from baseline EGG parameters related to VAS of nausea at each recording time interval (pre-and 10, 20 and 30 min after water load) at Day 4:
To assess the effect of exenatide on GE	<ul style="list-style-type: none"> Change from baseline of time to half gastric emptying (GEt_{1/2}) at Week 5 and 8 Change from baseline of profiles of ¹³C excreted in breath (kPCD¹) at Day 5 and at each time interval (45, 90, 120, 150, 180 and 240 min).
To assess the volume of water ingested during EGG	Change from baseline of volume of water ingested during EGG with water load test at Day 4.
To evaluate the effect of exenatide on stomach fullness, hunger, bloating and abdominal pain during EGG with water load test	Change from baseline of VAS of stomach fullness, hunger, bloating and abdominal pain during the EGG water load test at each time interval (pre-and 10, 20 and 30 min after water load) at Day 4

Objectives	Endpoints
Exploratory	
To evaluate safety and tolerability of exenatide	<ul style="list-style-type: none"> Vital signs, clinical laboratory tests, AEs, and GCSI-DD. Nausea AEs presenting outside the timing of the WLT and GCSI-DD.
To evaluate change in gastric rhythm status (Data permitting)	<ul style="list-style-type: none"> At Weeks 2, 5, and 8; over 30 min and at each time interval (pre-and 10, 20 and 30 min after water load). <ul style="list-style-type: none"> Number and % of subjects with a shift in gastric rhythm status. Number and % of subjects by gastric rhythm status. Mean and mean change from baseline in average dominant frequency

1. Percent dose excreted of ^{13}C *1000

3.2. Part B: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of albiglutide on GMA compared to exenatide	<ul style="list-style-type: none"> Change from baseline in EGG parameters at Weeks 2, 5, and 8 at each time interval (pre-and 10, 20 and 30 min after water load) <ul style="list-style-type: none"> Distribution of average power by frequency region (as % of power) Ratios of average power post-WLT/pre-WLT by frequency region Percentage (%) of time with the dominant EGG frequencies in the four frequency ranges (bradygastria, normal, tachygastria and duodenal) Change from baseline in EGG parameters related to VAS of nausea at Week 2, 5, and 8 at each time interval (pre-and 10, 20 and 30 min after water load)
Secondary	
To assess the effect of albiglutide on GE compared to exenatide	<ul style="list-style-type: none"> Change from baseline of time to half gastric emptying ($\text{GET}_{1/2}$) at Weeks 5 and 8 Change from baseline of profiles of ^{13}C excreted in breath (kPCD^1) at Weeks 5 and 8 and at each time interval (45, 90, 120, 150, 180 and 240 min)

Objectives	Endpoints
To assess the effect of albiglutide on the volume of water ingested during EGG compared to exenatide	Change from baseline of volume of water ingested during water load EGG test at, Weeks 2, 5 and 8.
To evaluate the effect of albiglutide on stomach fullness, hunger, bloating and abdominal pain during EGG with water load test compared with exenatide	Change from baseline of VAS of stomach fullness, hunger, bloating and abdominal pain during the EGG water load test at each time interval (pre-and 10, 20 and 30 min after water load) at Weeks 2, 5, and 8.
To evaluate safety and tolerability of albiglutide and exenatide	<ul style="list-style-type: none"> Vital signs, clinical laboratory tests, AEs, and GCSI-DD. Nausea AEs presenting outside the timing of the WLT and GCSI-DD.
Exploratory	
To evaluate change in gastric rhythm status (Data permitting)	<ul style="list-style-type: none"> At Weeks 2, 5, and 8; over 30 min and at each time interval (pre-and 10, 20 and 30 min after water load). <ul style="list-style-type: none"> Number and % of subjects with a shift in gastric rhythm status. Number and % of subjects by gastric rhythm status. Mean and mean change from baseline in average dominant frequency

1. Percent dose excreted of ^{13}C *1000

4. STUDY DESIGN

The study will be conducted in two phases (Part A and Part B). The study results from Part A will be evaluated and a decision to progress to Part B will be made based on the confirmation that change in GMA caused by the administration of exenatide is detectable by an EGG with WLT.

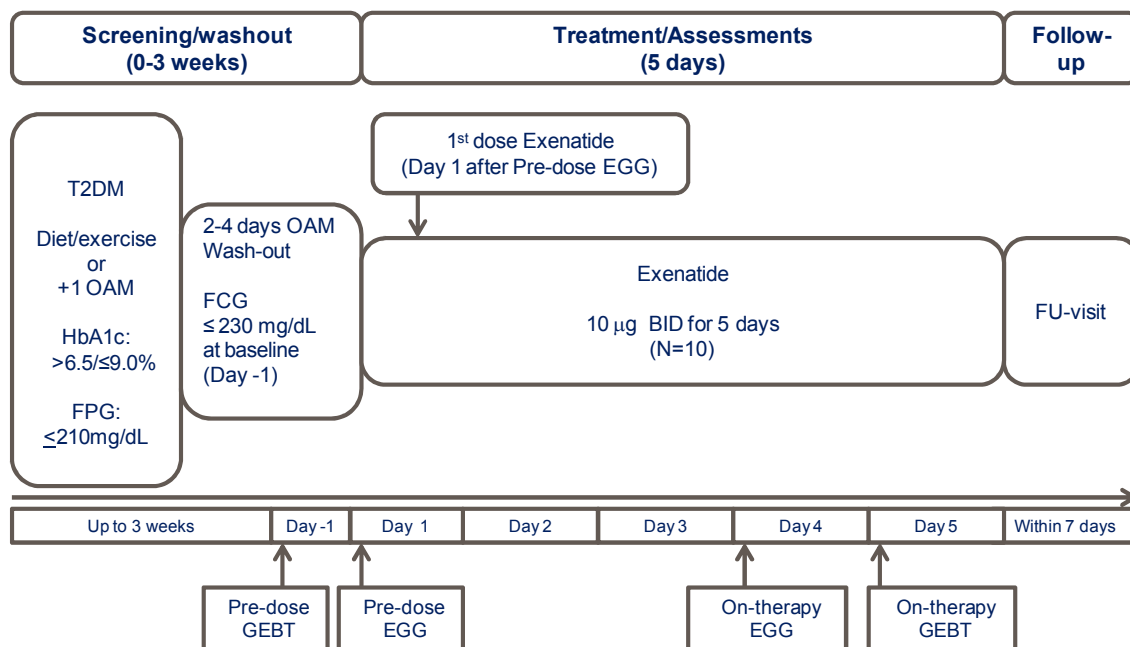
4.1. Part A: Study Design

4.1.1. Overall Design

- Part A is a single arm, open label pilot phase to evaluate the effect of 5-day repeated doses of exenatide (10 µg twice daily) on GMA, GE and nausea in subjects with T2DM.
- Part A will comprise 3 study periods (Figure 1.): screening/wash-out (up to 3 weeks), treatment (5±1 days), and post-treatment follow-up (within 7 days after the last dose of exenatide).
- Part A will recruit subjects with T2DM (>6 months since diagnosis) with HbA_{1c} >6.5% and ≤9.0%, FPG ≤210 mg/dL (central lab) at screening and on a current regimen of diet and exercise or a stable dose of one OAM (maintained for ≥ 2 months prior to screening).

- Fasting capillary blood glucose will be confirmed to be ≤ 230 mg/dL at baseline (see Section 5.3).
- Subjects receiving monotherapy with an OAM of metformin, sulfonylurea, sodium-glucose co-transporter-2 (SGLT2) inhibitors, or meglitinide at screening will be washed out for 2 days for immediate release and 4 days for extended release OAM prior to baseline.
- A subject's nutritional plan will be optimized following screening and maintained during the entire study.
- All evaluations and assessments will be performed as outpatient visits.
- Subjects will undergo 2 EGG and 2 GEBT assessments.
- At the end of the Part A subjects previously on an OAM will restart OAM at the discretion of the investigator after the last dose of exenatide. The half-life of exenatide (2-3 hours) should be taken into consideration (see Section 6.9).
- An overview of the study design for Part A is provided in Figure 1.

Figure 1 Study Schematic for Part A



Note: Two day washout for immediate release and 4 day washout for extended release OAMs. FCG; fasting capillary blood glucose.

4.1.2. Treatment Arms and Duration

Part A is a single arm design. All subjects will receive 10 µg subcutaneous exenatide twice daily for 5±1 days. The total duration of a subject's participation will be approximately 5 weeks.

4.1.3. Number of Subjects

- A sufficient number of subjects with T2DM will be screened and enrolled to achieve approximately 10 evaluable subjects.
- If subjects prematurely discontinue the Part A, additional replacement subjects may be enrolled at the discretion of the Investigator in consultation with the Sponsor.

4.2. Part A Data Review

Once Part A is complete, data will be reviewed and a decision to progress to Part B will be made. Adjustments to the study design of Part B (e.g., endpoint evaluation and/or number of subjects) may be made prior to progression to Part B. A decision to progress to Part B will be made based on the confirmation that change in GMA caused by the administration of exenatide is detectable by an EGG with WLT. Confirmation of safety when adding the WTL on top of a GLP1 receptor agonist will be required to progress to Part B. Details will be described in the RAP.

Changes resulting from Part A review including refinement of endpoints and statistical assessment of the endpoints will be incorporated in the RAP and will not be considered an amendment to the Protocol.

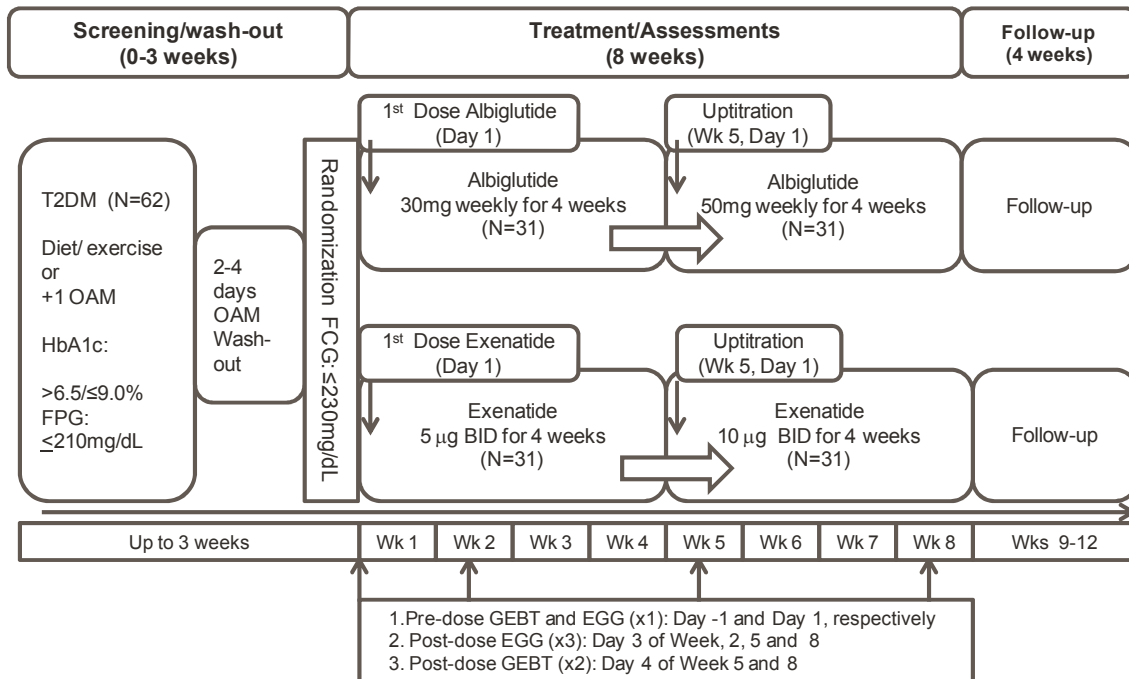
4.3. Part B: Study Design

4.3.1. Overall Design

- Part B is randomized, open-label, multicenter, active-controlled parallel group, study of 8 weeks treatment duration to compare the effects of albiglutide on GMA, GE and nausea as measured by VAS with exenatide as a positive control. The central readers of EGG and GEBT tests will be blinded to assigned treatments.
- Part B will comprise 3 study periods ([Figure 2](#)): screening/wash-out (up to 3 weeks), treatment (8 weeks), and post-treatment follow-up (4 weeks).
- Part B will recruit subjects with T2DM (>6 months since diagnosis) with HbA_{1c} >6.5% and ≤9.0%, FPG ≤210 mg/dL (central lab) at screening and on a current regimen of diet and exercise or a stable dose of one OAM (maintained for ≥ 2 months prior to screening).
- Fasting capillary blood glucose will be confirmed to be ≤230 mg/dL at baseline (see [Section 5.3](#)).
- Subjects participating in Part A are not allowed to participate in Part B.
- Subjects receiving monotherapy with an OAM of metformin, SGLT2-inhibitor, sulfonylurea or meglitinide will be washed out for 2 days for immediate release and 4 days for extended release OAM prior to randomization.
- A subject's nutritional plan will be optimized following screening and maintained during the entire study.
- All evaluations and assessments will be performed as outpatient visits.

- Subjects will undergo 4 EGG and 3 GEBT assessments.
- At randomization, subjects will be stratified by screening HbA1c value ($<7.5\%$ and $\geq 7.5\%$), and background use of OAM (OAM use versus no OAM use). Additional stratification may be added based on the results from Part A.
- At the end of the Part B subjects previously on an OAM will restart OAM at the discretion of the investigator after the last dose of study treatment. The half-life of albiglutide/exenatide should be taken into consideration (see Section 6.9).
- An overview of the study design for Part B is provided in Figure 2.

Figure 2 Study Schematic for Part B



Note: Two day washout for immediate release and 4 day washout for extended release OAMs.
FCG; fasting capillary blood glucose

4.3.2. Treatment Arms and Duration

- Subjects will be randomized in a 1:1 ratio to either albiglutide or exenatide.

Medication	Albiglutide Group	Exenatide Group
Albiglutide or Exenatide	After Baseline EGG on Day 1: once weekly SC injection at 30 mg for 4 weeks. From Week 5 Day 1: uptitrate to 50 mg once weekly SC injection for 4 weeks	After Baseline EGG on Day 1: twice daily SC injection at 5 µg for 4 weeks. From Week 5 Day 1: uptitrate to 10 µg twice daily SC injection for 4 weeks

SC = subcutaneous

- Total duration of a subject's participation will be approximately 15 weeks

- Down-titration (dose reduction) of albiglutide or exenatide is **NOT** permitted (see Section 6.3). If a subject experiences tolerability issues then the subject may be withdrawn from the study at the discretion of the investigator.
- During the study, any potential events of pancreatitis will be adjudicated by an independent pancreatitis adjudication committee (PAC) (Section 10.8).

4.3.3. Number of Subjects

- Approximately 62 subjects with T2DM will be randomized. Assuming 20% of subjects maybe withdrawn or lost to follow-up this will allow for 50 evaluable subjects (25 evaluable subjects per treatment group).

4.4. Design Justification

- This study is designed to gain insight into a potential peripheral mechanism of nausea associated with GLP-1R agonists and to determine if this mechanism can explain the clinically observed difference in GI tolerability between albiglutide and exenatide in clinical trials. This study will compare the effect of albiglutide and exenatide on GMA, GE and VAS of nausea in T2DM subjects.
- The study population, indication and doses of albiglutide and exenatide used in this study are consistent with the approved prescribing information (PI) for albiglutide and exenatide, respectively.
- The treatment duration will allow the evaluation of GMA, GE and VAS of nausea at expected steady-state and over time for both medications.
- EGG, GE and VAS of nausea will be assessed at the timing of expected C_{max} .
- Exenatide, a short acting GLP-1R agonist is used as a positive control. In the exenatide Phase 3 program, nausea was reported in up to 44% of subjects receiving exenatide [Byetta, US Prescribing Information, 2015]. Clinical data comparing albiglutide with exenatide is available from the albiglutide Phase 2b study [Rosenstock, 2009].
- The response of GMA to GLP-1R agonists has not been characterized in humans. Therefore, the study will be conducted in two phrases (Part A and Part B). Part A will characterize the effects of exenatide on GMA, GE, and nausea and confirm exenatide as a positive control for Part B. Part B will compare the effects of albiglutide to exenatide on GMA, GE and nausea.

4.5. Dose Justification

The use of albiglutide and exenatide in the study starting with 30 mg and 5µg, respectively is consistent with the recommended starting doses according to PIs for albiglutide and exenatide, respectively. Escalation to 50 mg and 10µg is also consistent with the maximal approved doses in clinical practice for both products. This dosing approach will give the opportunity to assess and provide clinically meaningful data on nausea gastric mechanisms for the available regimens that clinicians prescribe to their patients.

Albiglutide

Phase 3 studies confirmed the glycemic efficacy of both 30 mg and 50 mg doses of albiglutide, and both were generally well-tolerated. Although the 30 mg dose was effective at controlling glycemia for at least 2 years in many subjects with T2DM, an increase in dose to 50 mg weekly offered additional benefit without additional significant safety issues [See Investigator Brochure (IB) for further details].

Exenatide

Exenatide is approved to be initiated at 5 µg administered twice daily at any time within the 60-min period before the morning and evening meals. Based on clinical responses in clinical practice, the dose of exenatide can be increase to 10 µg bid.

4.6. Benefit:Risk Assessment

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

Summaries of findings from both clinical and non-clinical studies conducted with the albiglutide (GSK716155) can be found in the IB and in the US PI [[Tanzeum](#), US Prescribing Information, 2015].

Summaries of findings from both clinical and nonclinical studies conducted with exenatide can be found in the PI [[Byetta](#), US Prescribing Information, 2015].

The following sections outline the risk assessment and mitigation strategy for this protocol.

4.6.1. Risk Assessment

Key identified and potential risks associated with the administration of albiglutide or exenatide, study participation or study procedures, and the mitigation strategies for key risks of clinical significance are summarized in [Appendix 2](#).

For albiglutide, please also refer to the IB and any IB supplements as well as the complete Guidance for the Investigator and the US PI [[Tanzeum](#), US Prescribing Information, 2015]. For exenatide refer to the US PI [[Byetta](#), US Prescribing Information, 2015].

4.6.2. Benefit Assessment

Both albiglutide and exenatide have been approved in the US as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The clinical data from the albiglutide Phase 3 development program showed that once-weekly albiglutide treatment (both with the 30 mg and 50 mg doses) resulted in clinically relevant lowering of HbA_{1c} and FPG in subjects with T2DM. The clinical data from the exenatide Phase 3 development program indicated that 5 µg bid for a month followed by 10 µg bid resulted in clinically relevant lowering of HbA_{1c} and FPG in subjects with T2DM [Byetta, US Prescribing Information, 2015].

In Part A, eligible subjects will only receive exenatide for 5±1 days; the benefit in glycemic control is expected to be minimal due to this short period of treatment.

In Part B, subjects receiving study treatment (albiglutide or exenatide) as an adjunct to diet and exercise are expected to show beneficial reductions in HbA_{1c} and FPG.

All subjects will receive diet and exercise advice reinforced at each visit, and medical examination at screening and follow up visits at no cost.

4.6.3. Overall Benefit:Risk Conclusion

Measures to minimize risks provide protection to the subjects. The relatively short duration of both Part A and Part B of the study may not allow the subjects to experience the full benefit of treatment in glycemic control typically observed in clinical practice on treatment with albiglutide or exenatide. Data from this study will contribute to the overall knowledge of the benefit-to-risk profile of albiglutide and exenatide. The results may help physicians to better understand T2DM, treatment for T2DM and the mechanism of GI tolerability (nausea) with study medications.

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/IB supplement(s) and US PI [Tanzeum, US Prescribing Information, 2015] for albiglutide and the US PI for exenatide [Byetta, US Prescribing Information, 2015].

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

5.1. Inclusion Criteria

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

AGE
1. Between 18 and 60 years of age at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
<ol style="list-style-type: none"> 2. T2DM diagnosed at least 6 months prior to screening. 3. Subjects treated with diet and exercise alone or stable dose of single OAM of metformin, sulfonylurea (except chlorpropamide), SGLT2-inhibitor, or meglitinide for at least 2 months prior to screening. 4. HbA1c >6.5% and ≤9.0% at screening. If the first HbA1c value does not meet eligibility criterion, the HbA1c may be rechecked once during screening. If the average of these determinations meets the criterion, the subject is eligible. 5. FPG ≤210 mg/dL (central lab) at screening. If the first FPG value does not meet eligibility criterion, the FPG may be rechecked once during screening. 6. Patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM 2.0-S, Appendix 3) at screening: <ul style="list-style-type: none"> • Overall score ≤20 (if score is ≥21 and ≤25, subjects can be re-evaluated 2 weeks later) • Total score of items 1-9 is ≤9 • Score from any of single item ≤2

WEIGHT
7. Body mass index (BMI) >20 kg/m ² and <35 kg/m ² and a stable weight (no more than 5% reported change within 3 months prior to screening).

SEX
<ol style="list-style-type: none"> 8. Male or female. 9. 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: <ol style="list-style-type: none"> a) Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (eg., combined oral contraceptive pill; see Appendix 4) 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.

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.

REGULAR AND OTHER MEDICATIONS

10. For the regular use of other medications (does not include medications excluded by the protocol), subjects must be on a stable dose for at least 4 weeks before screening.

INFORMED CONSENT

11. Capable of giving signed informed consent; which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

1. Type 1 diabetes mellitus
2. T2DM treated with more than one OAM or with chronic use of insulin within 3 months prior to screening
3. Hemoglobin <11 g/dL (<110 g/L) for male subjects and <10 g/dL (<100 g/L) for female subjects at screening
4. Fasting triglyceride level >500 mg/dL at screening
5. Hemoglobinopathy that may affect proper interpretation of HbA_{1c}
6. History of cancer that has not been in full remission for at least 3 years before screening. (A history of squamous cell or basal cell carcinoma of the skin or treated cervical intra-epithelial neoplasia I or II is allowed).
7. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN-2).
8. History of acute or chronic pancreatitis.
9. History or current severe lactose intolerance

10. History of thyroid dysfunction or an abnormal (i.e., outside the normal reference range) thyroid function test assessed by thyroid stimulating hormone (TSH) at screening.
11. Alanine aminotransferase (ALT) >2.5x upper limit of normal (ULN).
12. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
13. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

NOTES:

- Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.

14. Clinical diagnosis of gastroparesis.
15. History of significant gastrointestinal medical conditions such as chronic esophagitis, peptic ulcer diseases, celiac disease, inflammatory bowel disease, unexplained abdominal pain or irritable bowel syndrome and/or history of surgery that in the opinion of the investigator is likely to significantly affect upper gastrointestinal or pancreatic function (e.g., gastric bypass, gastric banding, antrectomy, Roux-en-Y bypass, gastric vagotomy, small bowel resection, or surgeries thought to significantly affect upper GI function).
16. History of hypoglycemia unawareness (i.e., the absence of autonomic warning symptoms before the development of neuroglycopenic symptoms such as blurred vision, difficulty speaking, feeling faint, difficulty thinking, and confusion).
17. Diabetic complications (e.g., active proliferative retinopathy or severe diabetic neuropathy) or any other clinically significant abnormality (including a psychiatric disorder) that, in the opinion of the investigator, may pose additional risk in administering the investigational product or may influence data interpretation.
18. Clinically significant cardiovascular (CV) and/or cerebrovascular disease at any time, such as prior MI, unstable angina, stroke, transient ischemic attack or documented heart failure, before screening.
19. Estimated glomerular filtration rate (eGFR) $eGFR \leq 75 \text{ mL/min/1.73 m}^2$ [calculated using the Modification of Diet in Renal Disease (MDRD) formula] at screening.
20. Lung diseases associated with pulmonary dysfunction (e.g. chronic obstructive pulmonary disease).
21. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied should be excluded unless the investigator (in consultation with the Medical Monitor, if necessary) decides and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or ability to interpret study results.

CONCOMITANT MEDICATIONS

22. Unable to refrain from medications that might modify GMA or gastrointestinal motility, such as prokinetics (e.g., erythromycin), anti-emetics (e.g., metoclopramide), narcotics (e.g., morphine), anticholinergics (e.g., domperidone),

anti-acids (e.g., proton pump inhibitors, H2 blockers) and laxatives, received within 7 days prior to screening or high likelihood of a requirement during the study.

23. Use of oral or systemically injected glucocorticoids within the 3 months prior to randomization or high likelihood of a requirement for prolonged treatment (>1 week) in the 4 months following randomization. However, short courses of oral steroids (single dose or multiple doses for up to 7 days) may be permitted provided these cases are discussed with the Medical Monitor. Inhaled, intra-articular, epidural, and topical corticosteroids are allowed.

CONTRAINDICATIONS

24. Known allergy to albiglutide, exenatide or any product components (including yeast and human albumin), any other GLP-1 analogue, or other study treatment excipients OR other contraindications (per the PI) for the use of potential study treatment.
25. Intolerance or allergy to any component of gastric emptying test meal

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

26. Received any GLP-1R agonist at any time
27. Receipt of any investigational drug within the 30 days or 5 half-lives, whichever is longer, before screening, a history of receipt of an investigational antidiabetic drug within the 3 months before randomization.
28. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.

5.3. Additional Inclusion Criteria for Randomization

Subjects must have fasting capillary blood glucose ≤ 230 mg/dL on Day -1 (baseline) or randomization. If fasting capillary blood glucose is > 230 mg/dL, the test should be repeated immediately on the same day. If the average of the 2 values of fasting capillary blood glucose is ≤ 230 mg/dL, the subject can enter the study. If the average of the 2 values of fasting capillary blood glucose is > 230 mg/dL, then subject can be re-tested once as described above on a different day within the screening period.

5.4. Screening/Randomization Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.1.6).

5.5. Withdrawal/Stopping Criteria

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

Any subject experiencing the following will be required to discontinue study treatment 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 (see Section 7.4.1.5).
 - Pancreatic cancer.
 - Confirmed MTC or other thyroid C-cell neoplasia.
 - Liver chemistry abnormalities exceeding the threshold criteria outlined in Section 5.5.1
 - Severe allergic/hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or that are not reasonably attributable to another cause (see Section 7.4.1.5).
 - Recurrent hypoglycemia during the treatment period posing a potential risk to the subject, as judged by the investigator.
- Fasting capillary blood glucose ≥ 270 mg/dL after randomization on 3 consecutive days confirmed by central laboratory FPG (to be done within 1 week of the home glucose monitoring).
- eGFR $< 60 \text{ mL/min/1.73 m}^2$ (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).
- Non compliance with study treatment. If a subject misses one dose of albiglutide or 14 doses of exenatide, the investigator should contact the Medical Monitor, who will make a decision (on a case by case basis) on whether the subject should be withdrawn from the study for non compliance.
- 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 for next day.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

Subjects who are withdrawn or discontinue active participation in the study will no longer receive the randomized study treatment. Immediately upon discontinuation from active participation in this study, these subjects should complete the early withdrawal assessments and return for follow-up assessments (within 7 days for Part A and 4 weeks for Part B; Time and Events Table Section 7.1). If the subjects are unable or unwilling to return for the follow-up assessments, GSK will make every effort to follow-up with the subjects or their physician or caregiver.

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.

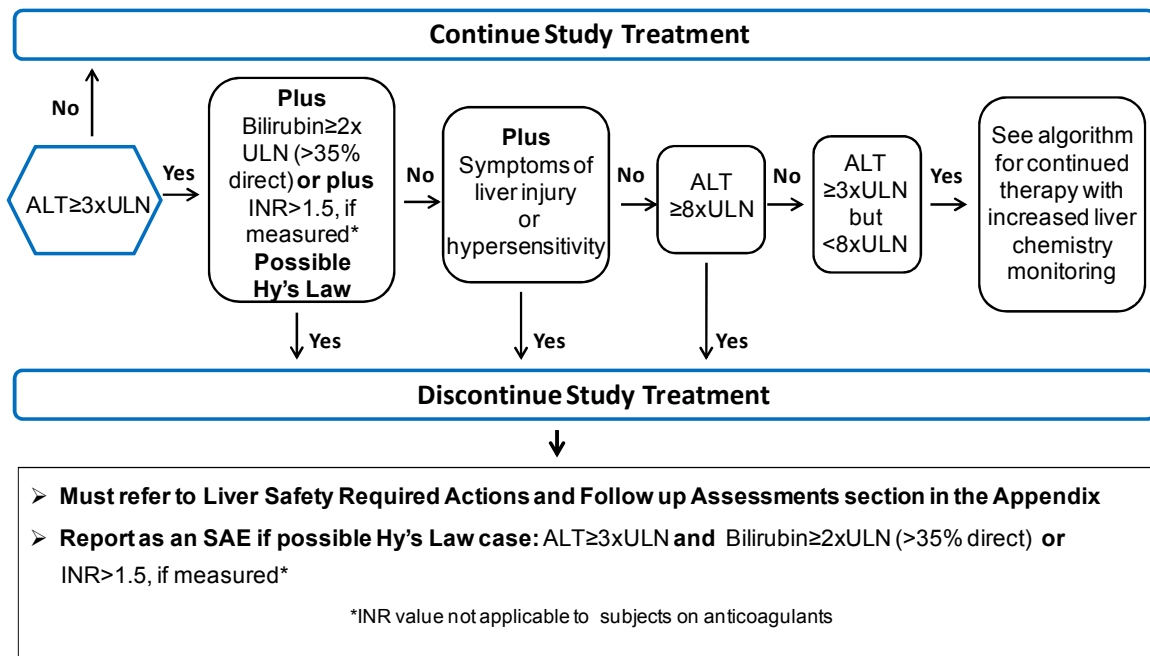
Early withdrawn subjects previously on an OAM will restart OAM at the discretion of the investigator. The half-life of albiglutide/exenatide should be taken into consideration (see Section 6.9).

Study medication withdrawal will require withdrawal from the study. Withdrawn subjects may be replaced in study Part A; replacement subjects will be enrolled at the discretion of the Investigator in consultation with the Sponsor. Withdrawn subjects will not be replaced in Part B.

5.5.1. Liver Chemistry Stopping Criteria

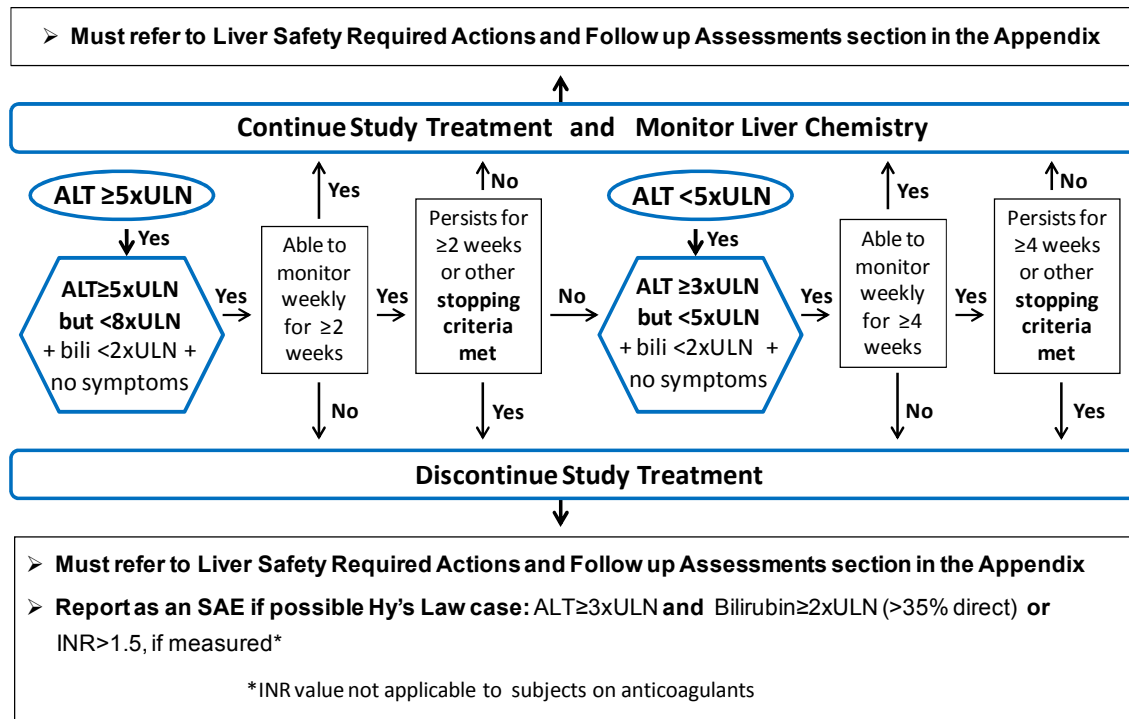
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the US Food and Drug Administration (FDA) premarketing clinical liver safety guidance). <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

Phase 3-4 Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 5](#)

Phase 3-4 Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3xULN$ but < 8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 5](#)

5.5.1.1. 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.

5.6. Subject and Study Completion

A completer for Part A is one who has completed all phases of the study described for Part A including the follow-up visit. A completer for Part B is one who has completed all phases of the study described for Part B including the follow-up visit.

Study Completion 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.

A description of the study treatments is provided in [Table 1](#)

Table 1 Study Treatment

Product name:	Study Treatment	
	Albiglutide (Tanzeum in US)	Exenatide (Byetta)
Formulation/Dosage form/Delivery system:	<p>Lyophilized albiglutide is provided as a fixed-dose, fully disposable pen injector system for delivery of the study treatment from a prefilled dual chamber cartridge (DCC) that is an integral part of the injector pen. It is designed for manual reconstitution of the dose, priming and insertion of the pen needle (29G), and manual injection.</p> <p>The DCC contains lyophilized albiglutide (30 mg or 50 mg). When the injector pen product is reconstituted a neutral, isotonic solution is produced. The pen delivers albiglutide in an injection volume of 0.5 mL.</p>	<p>Byetta (exenatide) is a marketed product of AstraZeneca Pharmaceuticals LP.</p> <p>Exenatide is supplied as sterile solution for injection containing 250 µg /mL exenatide.</p> <p>The following dose packages are available:</p> <ul style="list-style-type: none"> • 5 µg dose, 60 doses, 1.2 mL prefilled pen • 10 µg dose, 60 doses, 2.4 mL prefilled pen <p>Inactive ingredients include: metacresol, mannitol, glacial acetic acid, and sodium acetate trihydrate in water</p> <p>Refer to the current PI for further</p>

Product name:	Study Treatment	
	Albiglutide (Tanzeum in US)	Exenatide (Byetta)
	30 mg pen for injection contains 40.3 mg lyophilized albiglutide and 0.65 mL 50 mg pen for injection contains 67 mg lyophilized albiglutide and 0.65 mL water Inactive ingredients include: 153 mM mannitol, 0.01% (W/W) polysorbate 80, 10mM sodium phosphate, and 117 mM trehalose dehydrate in water	details.
Unit dose strength(s)/Dosage level(s):	30 mg or 50 mg	5µg or 10 µg per dose
Route of Administration	SC injection in the abdomen, thigh or upper arm region. Rotation of injection sites is recommended.	SC injection in the abdomen, thigh or upper arm region.
Dosing instructions:	Study Part A: not applicable Study Part B: 30 mg, weekly for 4 weeks, then uptitrated to 50 mg, weekly for 4 weeks Administered as a single SC injection once a week on the same day each week. Administered in the morning.	Study Part A: 10 µg twice daily for 5±1 days Study Part B: 5 µg twice daily for 4 weeks, then uptitrate to 10 µg for 4 weeks Administered as a SC injection within the 60-minute period before the morning and evening meals (or before the two main meals of the day approximately 6 hours or more apart). Exenatide should not be administered after a meal

6.2. Treatment Assignment

Part A:

All subjects in Part A of the study will receive 10 µg exenatide twice daily for 5±1 days.

Part B:

Randomized treatment assignment will be done via a web-based interactive response (IRT) system (RAMOS NG). Randomization will be centralized and will be implemented based on a randomization schedule generated by Clinical Statistics using RAMOS. Study center personnel will access the IRT to execute each randomization once a subject has

met all prerequisites for randomization and has completed all scheduled screening assessments.

Subjects will be assigned to study treatment in accordance with the randomization schedule. Eligible subjects will be stratified by screening HbA1c value ($<7.5\%$ and $\geq 7.5\%$), and background use of OAM (OAM use versus no OAM use). Additional stratification may be added based on the results from Part A.

Subjects will be randomized in a 1:1 ratio to either open label albiglutide or exenatide.

Study centre personnel will receive a randomization notification indicating only the unique subject identifier, the treatment assignment, and the date and time of randomization. Each subject number will be a unique identifier. Once a subject number has been assigned, the number will not be reused even if the subject withdraws before receiving any study treatment.

6.3. Planned Dose Adjustments

Part A:

There is no dose titration for Part A of this study.

Part B:

Subjects will receive 30 mg of albiglutide once weekly during Weeks 1-4 and will then be up-titrated to 50 mg albiglutide once weekly at Week 5 for the remainder of the study.

Subjects will receive 5 µg of exenatide twice daily during Weeks 1-4 and will then be up-titrated to 10 µg exenatide twice daily at Week 5 for the remainder of the study.

Down-titration (dose reduction) of albiglutide and exenatide is **NOT** permitted. If a subject experiences tolerability issues with the higher doses then the subject may be withdrawn from the study at the discretion of the investigator.

6.4. Blinding

This will be a treatment open-label study.

The reviewers/readers of EGG and individuals who perform sample testing and data production for GEBT will be blinded to randomized treatments. The study team will remain blinded to the treatment assigned group for the assessment of safety aggregate data. If an interim analysis is conducted (see Section 9.2.3.2.), the study team may be unblinded to the aggregate data.

6.5. Packaging and Labeling

Exenatide and albiglutide are marketed products. Exenatide will be sourced locally. Clinical image albiglutide pens will be provided. 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 or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled 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

Accountability will be done for the investigational product (albiglutide) and other study treatments (exenatide) at the time points specified in the Time and Events Table (Section 7.1) Subjects will be instructed to return all unused investigational product and used injector pens in order to perform drug accountability and determine compliance.

Acceptable overall compliance for IP (albiglutide) and other study treatments (exenatide) in this study will be $\geq 80\%$. Site personnel should confirm that subjects are taking their doses of albiglutide or exenatide, if appropriate, as prescribed by their physician. Adherence will be monitored for the duration of the study.

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

When subjects self-administer study treatment(s) at home, subjects will be instructed to return all unused investigational product and used injector pens. Compliance with albiglutide or exenatide will be assessed through a count of the returned injector pens and as reported by the subject. Compliance will be documented in the source documents and eCRF. Treatment start and stop dates, including dates for treatment delays will also be recorded in the eCRF.

6.8. Treatment of Study Treatment Overdose

In the event of an overdose the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the subject for AEs/serious adverse events (SAEs) that may be related to treatment overdose (see below). The appropriate supportive clinical care should be instituted, as dictated by the subject's clinical signs and symptoms.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.8.1. Albiglutide

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

During clinical studies of subjects with T2DM, the highest dose of albiglutide administered was 100 mg subcutaneously every 4 weeks for 12 weeks. This dose was associated with an increased frequency of nausea, vomiting, and headache.

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).

There is no specific antidote for overdose with albiglutide.

6.8.2. Exenatide

In a clinical study of exenatide, three patients with T2DM each experienced a single overdose of 100 µg SC (10 times the maximum recommended dose). Effects of the overdoses included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations. One of the three patients experienced severe hypoglycemia requiring parenteral glucose administration. The three patients recovered without complication.

Refer to the exenatide US PI for further details.

6.9. Treatment after the End of the Study

Investigational product will not be provided to subjects by GSK after the end of the study. In Part A, the last dose of exenatide will be in the morning before the GEBT on Day 5±1. In Part B, the last dose of exenatide will be in the morning before the GEBT of Week 8 Day 4±1. The last dose of albiglutide will be on Week 8 Day 1.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's T2DM. After the last dose of albiglutide or exenatide, the investigator will provide subjects with instructions of how to continue to treat their

T2DM after the end of the study. The half-life of his/her study treatment (albiglutide/exenatide) should be taken into consideration.

- The half-life of albiglutide is approximately 5 days, and significant therapeutic concentrations can persist for 3 to 4 weeks after discontinuation. The choice of other medicinal products and dose selection should be considered accordingly, as adverse reactions may continue and efficacy may, at least partly, persist until albiglutide levels decline.
- The half-life of exenatide is 2-3 hours.

6.10. Concomitant Medications and Non-Drug Therapies

All medications taken at any time from 3 months prior to screening to the follow-up visit will be recorded in the eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

Subjects on OAM at screening must discontinue OAM treatment as instructed in the protocol (see Section 4). After the last dose of albiglutide or exenatide, the investigator will provide subjects who were previously on an OAM with instructions of how and when to restart his/her OAM. The half-life of his/her study treatment (albiglutide/exenatide) should be taken into consideration (see Section 6.9).

6.10.1. Permitted Medications and Non-Drug Therapies

Unless specified as a prohibited medication in Section 6.10.2, all concomitant prescription or over the counter medications should be considered permitted provided they are not contraindicated in the albiglutide or exenatide (depending on study treatment) PI 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 and exenatide cause a delay in gastric emptying, and thereby have 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 US FDA-approved PI for all permitted medications.

6.10.2. Prohibited Medications and Non-Drug Therapies

Subjects must not use any of the following medications during the study (screening to end of treatment):

- Any antidiabetic medications (e.g., GLP-1R agonist, DPP-4 inhibitors, metformin, meglitinide, sulphonylurea, thiazolidinedione, SGLT2 inhibitors or insulin) other than the randomly assigned study treatment.
- Any investigational drug other than the study treatment they have been randomly assigned to.

- Oral or systemically injected corticosteroids (inhaled, intra-articular, epidural, and topical corticosteroids are allowed); short courses of oral steroids (single dose or multiple doses for up to 7 days) may be permitted provided these cases are discussed with the Medical Monitor.
- Antiretroviral drugs.
- Prescription and over-the-counter weight loss drugs.
- Any subject requiring medications that may produce or reduce nausea or significantly affect gastrointestinal motility such as prokinetics (e.g., erythromycin), anti-emetics (e.g., metoclopramide), narcotic analgesics (e.g., morphine), anticholinergics (e.g., domperidone), anti-acids (e.g., over the counter antacids, proton pump inhibitors, H2 blockers), laxatives and drugs affecting pancreatic or hepatobiliary systems.

If a subject receives a prohibited medication, the investigator should make the evaluation based on the reason (i.e., AE), duration of exposure and timings relative to the assessments in consultation with 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](#).

7.1. Time and Events Table

Table 2 Time and Events Table - Study Part A

Procedures	Screening/Wash-Out Period (0-3 Weeks)			Treatment Period (exenatide) (5 Days)					Un- schedule d	Early Withdrawal	Follow Up Within 7 Days
	-21 to Day -4	Day -3 to -5	Day -1 ¹³	Day 1	Day 2	Day 3	Day 4 ± 1 day ¹³	Day 5 ± 1 day ¹³			
Study Visit	1		2	3			4	5			6
Informed consent	X										
Inclusion and exclusion criteria	X		X ¹								
Demography, medical/disease history	X										
Enrolment into Treatment Phase				X							
OAM washout ²		X									
GEBT ³			X					X ¹²			
EGG /water load / VAS ³				X ¹¹			X ¹²				
ECG	X										
Vital Signs	X		X	X			X	X		X	X
Height, Weight, BMI	X										
Physical exam (F, Full; B, Brief) ⁴	F							B		B	
Concomitant medications review	X		X	X			X		X	X	X
AEs, SAEs, AEs of special interest review	X ⁵		X ⁵	X			X	X	X	X	X
PAGI-SYM ⁶	X										
GCSI-DD			X	X			X	X			
Chemistry, hematology, urinalysis, lipids ⁷	X							X		X	
HbA _{1c}	X										
FPG	X		X	X			X	X	X	X	X
Fasting capillary glucose at clinic ⁸			X	X			X	X			
Diet/Exercise/SMBG advice/reinforcement ⁹	X	X						X	X	X	X
Estradiol and FSH (females only: if required)	X										
Serum/Urine pregnancy test (FRP only)	S		U					U		U	U
TSH, Amylase and lipase	X										
Genetics sample ¹⁰				X							
RAMOS registration				X						X	X

Procedures	Screening/Wash-Out Period (0-3 Weeks)			Treatment Period (exenatide) (5 Days)					Un- schedule d	Early Withdrawal	Follow Up Within 7 Days
	-21 to Day -4	Day -3 to -5	Day -1 ¹³	Day 1	Day 2	Day 3	Day 4 ± 1 day ¹³	Day 5 ± 1 day ¹³			
Study Visit	1		2	3			4	5			6
Exenatide dosing				X ¹¹	X	X	X ¹²	X ¹²			
Study medication compliance				X			X	X			

1. **Before baseline assessment (Day -1)**, 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, **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. For subjects taking OAM at screening only. At a minimum, two day washout for immediate release and at minimum 4 day washout for extended release OAMs. See footnote 13. For information on restarting OAM refer to Section 6.9.
3. A small meal will be provided 2 hrs prior to the EGG procedure (Section 7.3.1). A meal will also be provided post-procedure for both the EGG and GEBT.
4. Details of full and brief physical examinations are provided in Section 7.4.3.
5. SAEs related to study participation only.
6. The GCSI-DD questionnaire will be completed after the standard AE questions have been answered.
7. Clinical chemistry, hematology, urinalysis and lipid assessments are described in Section 7.4.6. Lipids will be assessed at screening only.
8. Fasting capillary glucose will be measured prior to administration of exenatide. On GEBT (Day 5) or EGG (Day 1 and Day 4) assessment days, fasting capillary glucose will be measured prior to the GEBT or EGG procedure.
9. Subjects will be provided with diet and exercise guidance (see Section 7.4.8) and instructed on self monitoring blood glucose at screening (See Section 7.4.9). Subject will be instructed to bring in their glucometers at each visit for review. Diet/exercise/SMBG reinforced at subsequent visits.
10. Informed consent for optional genetic research should be obtained before collecting a sample.
11. On the morning of Day 1, subjects will receive instructions and training on exenatide self administration and will be monitored by medical staff at the clinic during administration of the first dose. The first dose of exenatide will be administered after the baseline EGG procedure and before the post-procedure meal.
12. On Day 4 and 5, the morning dose of exenatide will be administered at clinic 1 hr (±15 min) before the EGG or GEBT procedure.
13. Every effort should be made to schedule the procedures on the nominal visit day identified. However, in order to meet scheduling needs, subjects taking OAM can schedule Day-1 up to 3 days prior to Day 1 and the OAM stopped at least the day before the GEBT. For subjects treated with diet and exercise alone Day-1 can occur within 7 days prior to Day 1. The EGG and GEBT should not be scheduled on the same day

Table 3 Time and Events Table Study Part B

Procedures	Screening/Wash-Out Period (0-3 weeks)			Treatment Period (exenatide or albiglutide) (8 weeks)										Un scheduled	Early Withdrawal	Follow-Up	
Study Week	-3 to -1	-1 ¹⁶		1	2 ¹⁶	3	4	5 ¹⁶			6	7	8 ¹⁶			12	
Study Day	-21 to -4	-3 to -5	-1	1	10±1	-	-	29±1	31±1	32±1	-	-	52±1	53±1			78-84±3
Study Visits	1		2	3	4			5	6	7			8	9			10
Informed consent	X																
Inclusion and exclusion criteria	X		X ¹														
Demography, medical/disease history	X																
RAMOS registration				X				X								X	X
OAM washout ²		X															
GEBT ³			X							X ⁵				X ⁵			
EGG /water load / VAS ³				X ⁴	X ⁵				X ⁵				X ⁵				
ECG	X																
Vital Signs	X		X	X	X				X	X			X	X	X	X	X
Height, Weight, BMI	X													X ⁶		X ⁶	
Physical exam (F, Full; B, Brief) ⁷	F													B	B	B	B
Concomitant medications review	X		X	X	X			X	X	X			X	X	X	X	X
AEs, SAEs, AEs of special interest review	X ⁸		X ⁸	X	X			X	X	X			X	X	X	X	X
PAGI-SYM	X																
GCSI-DD ⁹			X	X	X				X	X			X	X			
Chemistry, hematology, urinalysis, lipids ¹⁰	X							X ¹¹						X		X	
HbA1c	X			X				X						X		X	
FPG	X		X	X	X			X	X	X			X	X		X	
Diet/Exercise/SMBG advice/reinforcement ¹²	X		X	X	X			X						X	X	X	X
capillary blood glucose at clinic			X	X	X			X	X	X			X	X		X	X
Estradiol and FSH (females only: if required)	X																
Serum/Urine pregnancy test (FRP only)	S				U			U						U		U	U
TSH, Amylase and lipase	X																
Genetics sample ¹³				X													
Randomization				X													
Dispense study medication				X				X									

Procedures	Screening/Wash-Out Period (0-3 weeks)			Treatment Period (exenatide or albiglutide) (8 weeks)										Un scheduled	Early Withdrawal	Follow-Up	
Study Week	-3 to -1	-1 ¹⁶		1	2 ¹⁶	3	4	5 ¹⁶			6	7	8 ¹⁶			12	
Study Day	-21 to -4	-3 to -5	-1	1	10±1	-	-	29±1	31±1	32±1	-	-	52±1	53±1			78-84±3
Study Visits	1		2	3	4			5	6	7			8	9			10
Study treatment administration training, (1 st dose & 1 st up-titration dose)				X ¹⁴				X ¹⁵									
Study treatment administration				X	X	X	X	X			X	X	X				
In clinic meal			X	X	X			X	X	X			X	X			
Study medication compliance				X	X			X	X	X			X	X			

1. **Before randomization**, 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, **do not randomize the subject** and contact the Medical Monitor to discuss how to proceed (e.g., to determine if repeat testing is warranted).
2. For subjects taking OAM at screening only. At a minimum, two day washout for immediate release and at a minimum 4 day washout for extended release OAMs. See footnote 16. For information on restarting OAM refer to Section 6.9
3. A small meal will be provided 2 hrs prior to the EGG procedure (Section 7.3.1). A meal will also be provided post-procedure for both the EGG and GEBT.
4. The Day 1 (baseline) EGG is to be conducted before administration of study medication.
5. The EGG must be scheduled 3±1 days after the albiglutide dose. The morning dose of exenatide will be administered at clinic 1 hr (±15 min) before the EGG or GEBT procedure.
6. Weight only
7. Details of full and brief physical examinations are provided in Section 7.4.3.
8. Only related to study participation SAEs
9. The GCSI-DD questionnaire will be completed after the standard AE questions have been answered.
10. Clinical chemistry, hematology, urinalysis and lipid assessments are described in Section 7.4.6. Lipids will be assessed at screening only.
11. Creatinine for eGFR only
12. Subjects will be provided with diet and exercise guidance (see Section 7.4.8) and instructed on self monitoring blood glucose at screening (See Section 7.4.9). Subject will be instructed to bring in their glucometers at each visit for review. Diet/exercise/SMBG reinforced at subsequent visits.
13. Informed consent for optional Genetic research should be obtained before collecting a sample.
14. On the morning of Day 1, after baseline EGG test, subjects will receive instructions and training on exenatide or albiglutide self administration and will be monitored by medical staff at the clinic during administration of the first dose. The first dose of will be administered after the baseline EGG procedure and before the post-procedure meal.
15. On Day 29 (± 1day), study treatment will be up-titrated to 10 µg twice daily exenatide or 50 mg once weekly albiglutide (see Section 6.3). Subjects will receive instructions and training on exenatide or albiglutide self administration and will be monitored by medical staff at the clinic during administration of the first dose.
16. Every effort should be made to schedule the procedures on the nominal visit day identified. However, in order to meet scheduling needs, subjects taking OAM can schedule Day-1 up to 3 days prior to Day 1 and the OAM stopped at least the day before the GEBT . For subjects treated with diet and exercise alone Day-1 can occur within 7 days prior to Day 1. The EGG and GEBT should not be scheduled on the same day.

7.2. Screening and Critical Baseline Assessments

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

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

Critical baseline assessments will include: GEBT, EGG.

Full details of screening and baseline assessments are provided in the Time and Events Table Section [7.1](#).

7.3. EGG and GEBT Test

GEBT and EGG measurements will be undertaken in the clinic and performed on separate days. Measurements for both Part A and Part B will be taken at the time points specified in the Time and Events Table in Section [7.1](#). Clinical visits for EGG and GEBT will have a visit window of ± 1 day and should be planned to avoid days of expected holidays, weekends and vacations.

- Albiglutide should be self-administered in the morning 3 ± 1 days before the EGG procedure.
- Exenatide should be self-administered twice daily. In the morning of each test day, subjects should be instructed NOT to self-administer exenatide at home. The morning dose of exenatide on the day of in-clinic test must be administered by the site staff. The dose of exenatide should be administered 1 hr ± 15 min prior to the start of the EGG or GEBT procedure. Every effort should be made to administer at the same pre-procedure time at each visit for the same subject.

7.3.1. EGG

Subjects should have nothing to eat or drink from midnight prior to the EGG. Two hours before the EGG subjects will be provided one piece of toast and 4 US fluid ounces (120 mL) of apple juice. This provides a small amount of calories so subjects are not “starving” and also provides a consistent EGG baseline before the water load. Subjects should not have anything further to eat or drink until after the EGG procedure.

EGG is recorded with ECG-type electrodes placed on the surface of the epigastrium. The EGG signals are recorded on a strip chart for visual analysis and digitized simultaneously for computer analysis. The EGG recordings include a 15-min baseline tracing after which the subjects ingest water for 5-min until they perceive their stomach is full. All subjects will rate symptoms experienced immediately before and 10, 20 and 30 min after ingestion of the water.

A VAS (0-100 mm) will be used to assess the intensity of the following sensations: no nausea (0) to severe nausea (100), stomach empty (0) to stomach full (100), hunger (0) to

satiety (100) and no bloating (0) to severe bloating (100). The recording channel with the clearest electrogastrographic signal will be chosen for visual and computer analysis.

The details of test procedures for EGG with water load test are provided in the SRM.

7.3.2. GEBT

The GEBT should be administered after an overnight fast. No solid food should be consumed or vigorous activity undertaken within 8 hours prior to the test. Alcohol should not be ingested within 8 hours prior to testing. The individual being tested may consume a small amount of water up to 1 hour before the test, but not more than 4 fluid ounces. Coffee may enhance gastric motility and should not be consumed within 8 hours prior to testing. Subjects should not smoke/use tobacco products (e.g. chewing tobacco, nicotine gum) before or during administration of GEBT.

The GEBT will be conducted over a four-hour period. After an overnight fast, duplicate pre-meal breath samples will be collected in capped glass tubes. Subjects will then consume a standard GEBT meal containing ^{13}C -Spirulina. Breath samples will be collected periodically. All breath samples pre- and post-meal will be returned to a central laboratory for analysis by Gas Isotope Ratio Mass Spectrometry (GIRMS) to determine the ratio of $^{13}\text{CO}_2/^{12}\text{CO}_2$ in each sample. By measuring the change in this ratio over time as compared to the pre-meal value, the rate of $^{13}\text{CO}_2$ excretion can be calculated and the individual's gastric emptying rate determined.

The details of GEBT administration instructions and breath sample collection procedures will be provided in the SRM.

7.4. Safety

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

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

The definitions of an AE or SAE can be found in [Appendix 6](#).

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

Events of nausea, hunger, stomach fullness, bloating, and abdominal pain resulting from the water load test will be captured and reported as an endpoint through the VAS and will not be considered an AE. Any of these 5 events reported outside of the timings of the VAS collection should be recorded as an AE/SAE if meets the definition as noted in [Appendix 6](#).

7.4.1.1. 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 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in [Appendix 6](#).
- 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 6](#).

7.4.1.2. Method of Detecting AEs and SAEs

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

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5). Further information on follow-up procedures is given in [Appendix 6](#).

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in [Appendix 6](#) and all deaths, whether or not they are considered SAEs, specific 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 eCRFs 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 eCRF within one week of receipt of a CV Event data query prompting its completion.

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

7.4.1.5. AEs of Special Interest

In the Phase 3a 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 (see Section [7.4.9](#))
- Liver events
- CV events (see Section [7.4.1.4](#))
- Injection site reactions
- Potential systemic allergic reactions
- Pancreatitis
- MTC
- Diabetic retinopathy
- Pneumonia
- Atrial fibrillation/atrial flutter

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

- GI events
- Pancreatic cancer
- Malignant neoplasms
- Appendicitis

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

If a histopathologic analysis related to events of special interest is performed, a copy of the histopathology report and a discharge summary if the subject was admitted, or any available case summary (e.g. clinic letter), is to be provided to the Sponsor, if available.

Subjects with treatment emergent thyroid nodules should be referred to a specialist for evaluation in accordance with local treatment guidelines.

Subjects will be provided information detailing the symptoms of pancreatitis and will be instructed to hold study medication and contact the investigator immediately if they experience any of these symptoms. All cases of suspected pancreatitis will be referred to the PAC (see Section 10.8.1).

Subjects should also be closely monitored for signs of potential allergic or drug hypersensitivity reactions including anaphylaxis, angioedema, generalized urticaria, and other potential manifestations of systemic allergic or drug hypersensitivity reactions. A serum sample should be taken as soon as possible after any such event in order to measure antibody to the drug. Instructions for sample processing are provided in Section 7.6. These events should be reported as AEs or SAEs based on the clinical evaluation of the subject.

7.4.1.6. 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.

7.4.2. Pregnancy

- If a subject becomes pregnant during the study they should discontinue Investigational Product.
- Any pregnancy that occurs during study participation (i.e., from baseline/randomization through the end of the post-treatment follow-up period) must be reported using a clinical trial pregnancy form.
- If a pregnancy is reported then the investigator should inform GSK or designee within 2 weeks of learning of the pregnancy and should follow the procedures outlined in [Appendix 4](#).

7.4.3. Physical Exams

A full or brief physical examination will be performed at the time points specified in the Time and Events Table Section [7.1](#).

- A full physical examination will include, at a minimum, assessment of the skin (including injection site), head, eyes, ears, nose, throat, thyroid, respiratory system cardiovascular system, abdomen (liver and spleen), lymph nodes, central nervous system and extremities.
- Brief physical examination includes evaluation of skin (including injection site), respiratory system, cardiovascular system, abdomen (liver, spleen), and central nervous system
- Investigators should pay special attention to clinical signs related to previous serious illnesses
- Weight will be performed at the time points specified in the Time and Events Table Section [7.1](#). Height and body mass index will be measured and recorded at screening only. Height and weight should be measured with the subject in indoor daytime clothing with no shoes.

7.4.4. Vital Signs

For vital signs (blood pressure and pulse rate), a single measurement will be taken at the time points specified in the Time and Events Table (Section [7.1](#))

During visits when ECGs are scheduled, vital sign measurements will be taken after the completion of the ECG sampling. Subjects may be either in a semi-recumbent or seated position. During visits when ECGs are not scheduled, vital sign measurements will be taken while subjects are in a seated position after at least a 5-minute rest period. During visits where a blood draw is required, vital sign measurements will be taken prior to sample collection.

7.4.5. Electrocardiogram (ECG)

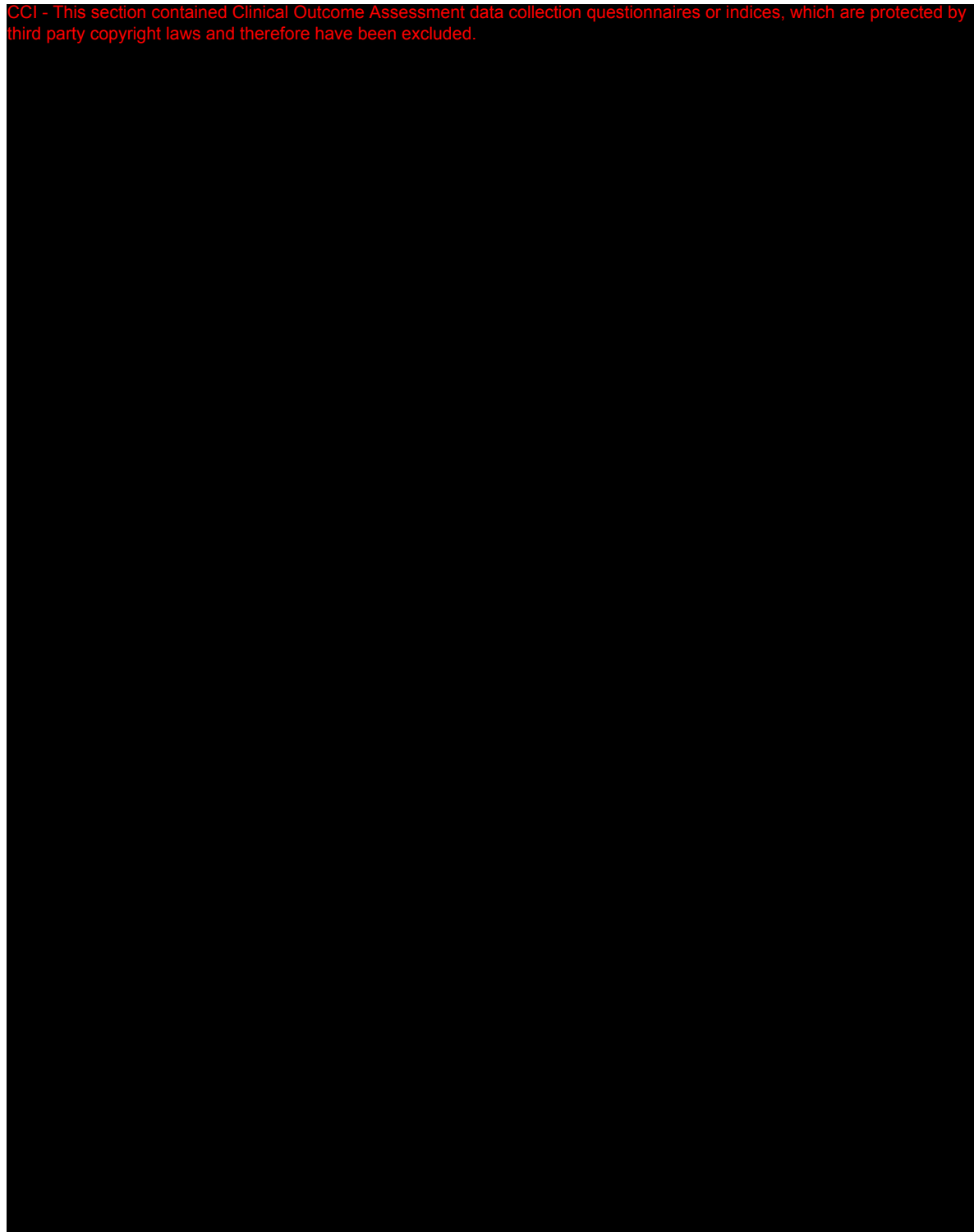
A single 12-lead ECG recording (with subject in semirecumbent position for 10 to 15 minutes before obtaining the ECG) will be performed at screening only using an ECG

machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

It is recommended that the ECGs be performed **before** measurement of vital signs and collection of blood samples for laboratory testing.

7.4.6. Gastroparesis Cardinal Symptom Index Daily Dairy (GCSI-DD)

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

7.4.7. 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. 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 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 with the exception of the fasting capillary blood glucose as noted in the Time and Events Table.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in [Table 4](#). Prior to the collection of blood samples, subjects should be **fasting** [no food or drink (except water) for at least 8 hours before sample collection]. During visits where ECGs and vital sign measurements are scheduled, blood samples will be collected after the completion of these assessments.

Table 4 Protocol Required Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	<ul style="list-style-type: none"> • Platelet count • RBC count • Hemoglobin • Hematocrit 	<ul style="list-style-type: none"> • <i>WBC count with Differential</i> • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils 	
Clinical Chemistry¹	<ul style="list-style-type: none"> • AST • ALT • GGT • BUN • Creatinine • eGRF (MDRD) 	<ul style="list-style-type: none"> • Bilirubin (total and direct/indirect) • Calcium • Magnesium • Potassium • Sodium 	<ul style="list-style-type: none"> • Phosphorous • Chloride • Albumin • Total protein
Urinalysis	<ul style="list-style-type: none"> • Specific gravity • Ketones • Leukocyte esterase • Microscopic examination (if blood or protein is abnormal) 	<ul style="list-style-type: none"> • pH • Blood • Microalbumin 	<ul style="list-style-type: none"> • Glucose • Nitrates • Creatinine
Glycemic parameters	<ul style="list-style-type: none"> • HbA1c 	<ul style="list-style-type: none"> • FPG 	<ul style="list-style-type: none"> • Fasting capillary glucose
Lipid parameters⁵	<ul style="list-style-type: none"> • Total cholesterol • Triglycerides 	<ul style="list-style-type: none"> • LDL-C (direct) 	<ul style="list-style-type: none"> • HDL-C
Other laboratory tests	<ul style="list-style-type: none"> • Serum pregnancy test² • Urine pregnancy test² • Amylase⁶ 	<ul style="list-style-type: none"> • FSH³ • TSH⁴ 	<ul style="list-style-type: none"> • Estradiol³ • Lipase⁶
<p>AST, aspartate transaminase; GGT, γ-glutamyltransferase; LDL-C, low density lipoprotein-C; HDL-C, high density lipoprotein-C; TSH, thyroid stimulating hormone, WBC, white blood cells</p> <ol style="list-style-type: none"> 1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.5.1 and Appendix 5. 2. For females of reproductive potential only. 3. . As needed in postmenopausal women were their menopausal status is in doubt (see Inclusion Criteria Section 5.1). 4. TSH screening only. If TSH is above the ULN, free T4 (reflex) will also be measured 5. Screening only. 6. Screening only. 			

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

7.4.7.1. FPG and HbA_{1c} Central Laboratory

HbA_{1c} and FPG will be measured at the time points specified in the Time and Events Table in Section 7.1. If subjects are scheduled to receive study treatment during an in-clinic visit, blood samples for HbA_{1c} and FPG should be collected before administration of study treatment.

7.4.7.2. Estimated Glomerular Filtration Rate (eGFR)

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

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

7.4.8. Diabetic Dietary Instruction and Exercise

Standard diabetic dietary and exercise guidance will be provided by the site at screening and reinforced at each study visit specified in the Time and Events Table in Section 7.1.

7.4.9. Home Blood Glucose Monitoring

Home blood glucose monitoring advice as well as advice on the signs and symptoms of hypoglycemia will be provided by the site at screening and reinforced at each study site visit specified in the Time and Events Table in Section 7.1.

All subjects in the study will be recommended to measure and record/store blood glucose values using their glucose meter each morning before breakfast. At least one day per week, subjects should measure blood glucose values at the following times (except GEBT and EGG assessment days).

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

The investigator will review the glucose meter readings at each study visit and will decide the frequency of measurements based on the subject's individual needs.

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 (i.e. fasting capillary blood

glucose >270 mg/dL) or hypoglycemia (particularly if symptomatic) to the investigator (or his or her designee). Assessment and action should then occur as deemed appropriate by the investigator

7.4.9.1. Fasting Capillary Blood Glucose at clinical visits

Capillary blood glucose will be measured prior to the EGG and GEBT procedures and recorded in the eCRF at the time points specified in the Time and Events Schedule in Section 7.1.

7.4.10. Hyperglycemic Events

Subjects will be asked to report any hyperglycemic events, including time between study visits. Subjects requiring rescue therapy due to fasting plasma glucose ≥ 270 mg/dL confirmed by central lab will be withdrawn from the study. At investigator discretion, a subject may be withdrawn for hyperglycemia at any time for safety considerations, not necessarily reaching the threshold of fasting plasma glucose ≥ 270 mg/dL

7.4.11. 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 [[Sequist, 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 6](#)) should be categorized as outlined in this section and reported appropriately in the SAE eCRF page and the hypoglycemic events AE of special interest page.

7.5. Tracking of Albiglutide and Exenatide Pen Injector Failures and User Errors

All albiglutide pen injector failures and user errors must be detected, documented, and reported by the investigator throughout the study. Detailed information on albiglutide pen injector failures and user errors will be collected on the Albiglutide Injector Pen and Reporting Form.

For both, albiglutide and exenatide pen injector failures and user errors associated with or resulting in events fulfilling the definition of an AE or SAE will follow the processes outlined in [Section 7.4.1](#)

7.6. Immunogenicity

In the case of severe systemic allergic reactions that include anaphylaxis, angioedema, or other severe potential hypersensitivity reactions in subjects that have received albiglutide, that cannot reasonably be attributed to another cause, 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 contracted testing facility for specific immunological testing (albiglutide-specific immunoglobulin E and other tests, as appropriate). A follow-up serum sample will be taken 8 weeks after final dose of study treatment in these subjects.

Subjects with drug hypersensitivity reactions that are not reasonably attributable to another cause should be withdrawn from the study and should not be rechallenged with albiglutide (see [Section 5.5](#) and [Section 7.4.1.5](#)).

7.7. Genetics

Information regarding genetic research is included in [Appendix 7](#).

8. DATA MANAGEMENT

- For this study, subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- AEs and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug.
- 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. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Part A: Statistical Considerations and Data

9.1.1. Hypotheses

No formal statistical hypotheses are being tested in Part A. Part A will be a pilot phase investigating the effect of repeated doses of exenatide on GMA, GE, and VAS of nausea.

9.1.2. Sample Size Considerations

9.1.2.1. Sample Size Assumptions

Sample size for Part A is not based on formal sample size calculations; it is based on the anticipated minimum number to better estimate the effect of repeated doses of exenatide on GMA. The pivotal assessment of the repeated doses on GMA will be provided by Part B of the study, with Part A providing an exploratory assessment to support progression to Part B.

Approximately 10 evaluable subjects with T2DM will be enrolled in Part A of the study.

9.1.2.2. Sample Size Re-estimation or Adjustment

If subjects prematurely discontinue the Part A of the study or if the central data reader reports that the data is not valid, additional replacement subjects maybe enrolled at the discretion of the Investigator in consultation with the Sponsor.

9.1.3. Data Analysis Considerations

All protocol defined endpoints will be summarized using suitable displays.

9.1.3.1. Analysis Populations

For this exploratory study, the analysis set will include subjects who have valid data. Data will be assessed and reviewed by the central reader before it is considered valid. Additional details will be provided in the RAP.

9.1.4. Key Elements of Analysis Plan

9.1.4.1. Exploratory Analysis

No formal statistical analyses will be performed for the exploratory endpoints that are listed under Section 3.1. All exploratory endpoints will be assessed using descriptive statistics and graphical displays as appropriate.

9.1.4.2. Part A review

Changes resulting from Part A review including refinement of endpoints and statistical assessment of the endpoints will be incorporated in the RAP and will not be considered an amendment to the Protocol

9.2. Part B: Statistical Considerations and Data Analysis

9.2.1. Hypotheses

Hypotheses testing in Part B will be performed for the parameters listed in Section 3.2 to compare albiglutide to exenatide in subjects with T2DM for a treatment period of 8 weeks.

9.2.2. Sample Size Considerations

9.2.2.1. Sample Size Assumptions

Approximately 62 subjects (31 per arm) will be randomized in a 1:1 ratio to either albiglutide or exenatide. The study will target to have a total of approximately 50 evaluable subjects (25 subject per treatment arm) taking into account the assumed withdrawal rate of approximately 20%. The study is exploratory in nature and there is no similar published work available in the same indication and population to act as a guide. This sample size is based on feasibility and the sample size assumptions may be re-evaluated once Part A results are available.

9.2.2.2. Sample Size Re-estimation or Adjustment

Based on the results from Part A the total sample size for Part B may be adjusted, within the bounds of feasibility.

9.2.3. Data Analysis Considerations

9.2.3.1. Analysis Populations

For this exploratory study, the analysis set will include subjects who have valid data. Data will be assessed and reviewed by the central reader before it is considered valid. Additional details will be provided in the RAP.

9.2.3.2. Interim Analysis

This is an open-label exploratory study with sample-size based on feasibility considerations. To support monitoring of endpoint variability; data aggregated by treatment group may be reviewed by the Sponsor while the trial is ongoing.

9.2.4. Key Elements of Analysis Plan

9.2.4.1. Primary Analysis

The primary endpoint is change from baseline in EGG parameters at Week 2, 5, and 8 at each time interval (pre-and 10, 20 and 30 min after water load). The primary endpoint is change in GMA as assessed by EGG parameters: change from baseline of distribution of average power by frequency region (as % of power); change from baseline of ratios of average power post-water load test (post-WLT)/pre water load test (pre-WLT) by frequency region; and change from baseline of percentage (%) of time with the dominant EGG frequencies in the four frequency ranges (bradygastria, normal, tachygastria and duodenal). The primary analyses of the primary EGG parameters will be conducted using mixed-effect model with repeated measures (MMRM). The MMRM model will include the EGG parameter as the dependent variable; treatment group, time interval, visit week, and treatment-by-week interaction as fixed effects; the relevant parameter baseline as covariate; and subject as a random effect.

The primary endpoint of change from baseline in EGG parameters related to VAS of nausea at Week 2, 5, and 8 at each time interval (pre-and 10, 20 and 30 min after water load) will be analyzed using the MMRM method as described above. The MMRM model will include the EGG parameter as the dependent variable (the same EGG parameters as listed above); treatment group, time interval, visit week, and treatment-by-week interaction as fixed effects; the relevant parameter baseline as covariate; VAS of nausea as time varying covariate; and subject as a random effect.

Treatment effects estimates (and associated 95% CI) of albiglutide will be evaluated within this MMRM model as least squares means contrasts relative to exenatide. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion.

Part B analysis is further described in the RAP.

9.2.4.2. Secondary analyses

The relative effects of albiglutide compared to exenatide will also be assessed across a number of secondary endpoints. The secondary endpoints are defined in Section 3.2 and include change from baseline in $T_{1/2}$ at Week 5 and 8; change from baseline in kPCD of GE at Week 5 and 8 and at each time interval (45, 90, 120, 150, 180 and 240 min); change from baseline volume of water ingested during water load EGG test Week 2, 5 and 8; and change from baseline of VAS of stomach fullness, hunger, bloating and abdominal pain during the EGG water load test at Week 2, 5, and 8. The secondary endpoints will be analyzed analogous to the primary endpoint using MMRM. In addition, summary statistics (including number of subjects, mean, median, min, max, SD, SE) and graphical displays will be provided.

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

Vital signs, clinical laboratory tests, adverse events (AEs), Gastroparesis Cardinal Symptom Index – Daily Diary (GCSI-DD), and nausea AEs presenting outside the timing of the WLT and GCSI-DD will be assessed using descriptive statistics.

9.2.4.3. Exploratory analyses

The exploratory endpoint number and % of subjects with a shift in gastric rhythm status will be summarized descriptively by treatment group. In addition, the number and percentage of subjects by gastric rhythm status will be provided by time interval and visit. The mean and mean change from baseline in average dominate frequency will be summarized using descriptive statistics.

The details of any further planned analyses, including subgroup analysis, will be provided in the RAP. Moreover, the relationship between EGG parameters and FPG and HbA1c will be examined.

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

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

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki 2008 (which is based on the initial version enacted in 1996). This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent for each subject prior to participation in the study.
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK/designee will provide full details of the above procedures, either verbally, in writing, or both.

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/designee 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/designee 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/designee 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 Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK/designee site or other mutually-agreeable location.

GSK/designee 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

10.8.1. Pancreatitis Adjudication Committee

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.

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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)
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	creatine phosphokinase
cpm	cycles per minute
CV	cardiovascular
DCC	dual cartridge chamber
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase 4
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EGG	electrogastrogram
FDA	US Food and Drug Administration
FPG	fasting plasma glucose
FRP	females of reproductive potential
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GE	gastric emptying
GEBT	gastric emptying breath test
GGT	gamma glutamyl transferase
GI	gastrointestinal
GIRMS	Gas Isotope Ratio Mass Spectrometry
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
GMA	gastric myoelectrical activity
GCSI-DD	Gastroparesis Cardinal Symptom Index – Daily Diary
GSK	GlaxoSmithKline
HbA1c	glycated hemoglobin
hCG	human chorionic gonadotrophin
HDL-c	high density lipoproteins cholesterol
HRT	hormone replacement therapy
IB	Investigator's Brochure

ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRT	web-based interactive response system
ITT	intent-to-treat
LDH	lactate dehydrogenase
LDL-c	low density lipoproteins cholesterol
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MI	myocardial infarction
MMRM	mixed-effect model with repeated measures
MSDS	Material Safety Data Sheet
MTC	medullary thyroid cancer
OAM	oral anti-diabetic medication
PAC	Pancreatitis Adjudication Committee
PAGI-SYM	patient assessment of upper gastrointestinal symptom severity index
PK	pharmacokinetics
Pre-WLT	pre water load test
Post-WLT	post water load test
PI	Prescribing Information
RAP	Reporting Analysis Plan
RBC	red blood cell
SC	subcutaneous
SAE	serious adverse event
SGLT2	sodium-glucose co-transporter-2
SmPC	Summary of Product Characteristics
SRM	Study Reference Manual
T _{1/2}	Half-life
T2DM	type 2 diabetes mellitus
TSH	thyroid stimulating hormone
ULN	upper limit of normal range
VAS	Visual analogue scale
WBC	white blood cell

Trademark Information

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12.2. Appendix 2: Risk Assessment for Albiglutide (GSK716155) and Exenatide (Byetta)

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: (albiglutide (GSK716155) and exenatide (Byetta)) Identified Risks		
Pancreatitis	<p>Albiglutide:</p> <p>In clinical trials, acute pancreatitis has been reported in association with albiglutide and other GLP-1R agonists</p> <p>Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether these subjects are at increased risk for pancreatitis.</p>	<p>Subjects with a history of acute or chronic pancreatitis are excluded from entering the study (See Section 5.2)</p> <p>Subjects will be informed of the characteristic symptom of pancreatitis: persistent severe abdominal pain. If pancreatitis is suspected, albiglutide or exenatide should be promptly discontinued and if pancreatitis is confirmed, study treatment will not be restarted (see Section 5.5).</p> <p>Risk communication via guidance for investigators (see albiglutide IB or exenatide PI) and informed consent form for subjects.</p>
	<p>Exenatide:</p> <p>Exenatide has not been studied in subjects with a history of pancreatitis.</p> <p>Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.</p>	
Gastrointestinal (GI) events	<p>Albiglutide:</p> <p>Albiglutide has not been studied in subjects with severe GI disease, including severe gastroparesis.</p> <p>Use of albiglutide and other GLP-1R agonists may be associated with GI AEs (e.g., diarrhea, nausea, and vomiting)</p>	<p>Subjects with Clinically diagnosed gastroparesis or a history of significant gastrointestinal medical conditions are excluded from entering the study (See Section 5.2).</p> <p>Risk communication via guidance for investigators (see albiglutide IB or exenatide PI) and informed consent form for subjects.</p>
	<p>Exenatide:</p> <p>Exenatide has not been study in patients with severe gastrointestinal disease, including gastroparesis. Because Exenatide is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting and diarrhea, the</p>	

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	use of Exenatide is not recommended in patients with severe gastrointestinal disease.	
Hypoglycemia	Albiglutide: Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycemia; however, when used in combination with insulin secretagogues (such as sulphonylurea) or insulin, the risk of hypoglycemia is increased.	Self- monitoring of blood glucose for hypoglycemia and advice on treatment are included in the study. The risk of hypoglycemia in this study is anticipated to be low as study medications will be used as monotherapy. Risk communication via guidance for investigators (see albiglutide IB or exenatide PI) and informed consent form for subjects
	Exenatide: The risk of hypoglycemia is increased when exenatide is used in combination with a insulin, sulphonylurea or other glucose-independent insulin secretagogues (e.g. meglitinides).	
Immunogenicity (e.g., clinical sequelae of antidrug antibodies)	Albiglutide: In the Phase 3 program, approximately 5% of subjects developed anti-albiglutide antibodies, but based on available clinical data, anti-albiglutide antibody formation is not expected to impact the overall safety or efficacy of albiglutide treatment. Although most subjects with injection site reactions were antibody negative (approximately 85%), injection site reactions were reported more frequently for antibody-positive subjects (approximately 41%) than antibody-negative subjects (approximately 14%).	In the case of systemic allergic reactions that include anaphylaxis, angioedema, or other severe potential hypersensitivity reactions in subjects that have received albiglutide, that cannot reasonably be attributed to another cause a serum sample will be obtained for immunogenicity testing (see Section 7.6). Subjects with severe allergic reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology will be withdrawn from the study Risk communication via guidance for investigators (see albiglutide IB or
	Exenatide: Patients may develop antibodies following treatment with exenatide. Antibody measured in 90% of subjects. In 1-4% of these subjects, formation of antibody was associated with attenuated glycemic control.	

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
		exenatide PI) and informed consent form for subjects
Hypersensitivity Reactions	<p>Albiglutide:</p> <p>Hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase 3 program.</p> <p>Across 8 Phase 3 clinical trials, a serious hypersensitivity reaction with pruritus, rash, and dyspnea occurred in a patient treated with albiglutide.</p>	<p>Subjects with known allergy to any GLP-1 receptor agonist or excipients of albiglutide or exenatide are excluded from the study (See Section 5.2).</p> <p>Subjects with severe allergic/hypersensitivity reactions that are considered by the investigator to be attributable to investigational product or without a likely alternative aetiology will be withdrawn from the study</p> <p>Risk communication via guidance for investigators (see albiglutide IB or exenatide PI) and informed consent form for subjects.</p>
	<p>Exenatide:</p> <p>There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with Exenatide.</p>	
Injection site reactions	<p>Albiglutide:</p> <p>Albiglutide is given as an SC injection in the abdomen, thigh, or upper arm and may cause rash, erythema, and/or itching at the injection site.</p>	<p>Subjects will be advised that when injecting in the same region, to use a different injection site with each dose.</p> <p>Risk communication via guidance for investigators (see albiglutide IB or exenatide PI) and informed consent form for subjects.</p>
	<p>Exenatide:</p> <p>Injection-site reactions have been reported during post approval use of Exenatide .</p>	
Other adverse reactions	<p>Albiglutide:</p> <p>e.g. pneumonia, atrial fibrillation/atrial flutter, and appendicitis</p> <p>In the Phase 3 program, other adverse reactions were observed with a cumulative incidence of <3% in studies up to 3 years in duration.</p>	<p>Risk communication via guidance for investigators (see albiglutide IB or exenatide PI) and informed consent form for subjects</p>

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	<p>Exenatide:</p> <p>The following additional adverse reactions have been reported during postapproval use of exenatide: neurologic: dysgeusia; somnolence and alopecia</p> <p>Increases in international normalized ratio with concomitant use of warfarin sometimes associated with bleeding. And renal impairment sometimes requiring hemodialysis and kidney transplant.</p>	
<p align="center">Investigational Product: (albiglutide (GSK716155) and exenatide (Byetta))</p> <p align="center">Potential Risks</p>		
Thyroid C-cell tumors	<p>Albiglutide:</p> <p>This potential risk arises from nonclinical rodent studies where GLP-1R agonists have been associated with increases in serum calcitonin, thyroid C-cell focal hyperplasia, and C-cell tumors. The relevance of these observations to humans is uncertain.</p> <p>In Phase 3 studies of up to 3 years in duration, albiglutide was not associated with clinically relevant increases in serum calcitonin.</p>	<p>Subjects with a personal or family history of MTC or subjects with Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) are excluded from the study (See Section 5.2).</p> <p>Risk communication via guidance for investigators (see albiglutide IB or exenatide PI) and informed consent form for subjects</p>
	<p>Exenatide:</p> <p>A 104-week carcinogenicity study was conducted in male and female rats at doses of 18, 70 or 250 µg/kg/day administered by bolus SC injection, benign thyroid C-cell adenomas were observed in female rats at all exenatide doses.</p>	
Other malignant neoplasms (e.g., pancreatic cancer or malignancy when used in combination with insulin)	<p>Theoretical concern for pancreatic cancer associated with GLP-1–based therapies (DPP-IV inhibitors and GLP-1R agonists) is under evaluation by regulatory authorities [Egan, 2014] and has thus far concluded that a causal relationship cannot be established currently, but they will continue to investigate as more data become available.</p> <p>Theoretical concern raised by the European Union regulatory authorities is based</p>	Subjects on treatment with insulin are not eligible for the study and subjects requiring insulin will be withdrawn.

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	on their concern for the biological plausibility of a tumor-promoting effect when a GLP-1 agonist is combined with insulin.	
CV safety of antidiabetic therapy	<p>Albiglutide:</p> <p>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.</p> <p>In the Phase 3 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, MI, stroke, and hospitalization for unstable angina) with albiglutide versus all comparators (MACE+ hazard ratio = 1.00; 95% CI: 0.68, 1.49).</p>	<p>Subjects with clinically significant CV and/or cerebrovascular disease at any time before screening will be excluded from the study. Further details are provided in Section 5.2.</p> <p>See albiglutide IB or exenatide PI</p>
	<p>Exenatide</p> <p>There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with exenatide.</p>	
Hepatotoxicity	<p>Albiglutide:</p> <p>One subject in the Phase 3 clinical program developed a probable drug-induced liver injury with an asymptomatic elevation in ALT and total bilirubin, although the case had some atypical features and complicating factors.</p>	<p>Routine liver safety laboratory evaluations will be conducted and specific withdrawal criteria for elevated liver function tests have been defined (See Section 5.5.1).</p> <p>Risk communication via informed consent form for subjects</p>
	<p>Exenatide:</p> <p>No pharmacokinetic study has been performed in patients with diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide.</p>	

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: (albiglutide (GSK716155) and exenatide (Byetta)) Additional Considerations		
Patient population with severe renal impairment (eGFR <30 mL/min/1.73 m ²)	<p>Albiglutide:</p> <p>Experience in T2DM patients with severe renal impairment is very limited. Subjects with severe renal (eGFR <30 mL/min/1.73 m²) impairment receiving albiglutide experienced a higher frequency of diarrhea, nausea, and vomiting compared with subjects with mild/moderate renal impairment.</p>	<p>Subjects with an eGFR ≤75mL/min/1.73 m² (calculated using the MDRD formula) are excluded from the study (see Section 5.2).</p> <p>Risk communication via guidance for investigators (see Section 6 of the IB) and informed consent form for subjects.</p>
	<p>Exenatide:</p> <p>Exenatide should be not be used on patients with severe renal impairment (eGFR <30 mL/min/1.73 m²). There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometime requiring hemodialysis or kidney transplantation.</p>	

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Drug interactions	<p>Albiglutide:</p> <p>Albiglutide causes a delay in gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications.</p> <p>Drug interaction studies have been conducted with digoxin, warfarin, oral contraceptives, and simvastatin, which demonstrated no clinically relevant PK or PD effects.</p>	Risk communication via guidance for investigators (see albiglutide IB or exenatide PI) and informed consent form for subjects
	<p>Exenatide:</p> <p>The effect of Exenatide to slow gastric emptying can reduce the extent and rate of absorption of orally administered drugs. Exenatide should be used with caution in patients receiving oral medications that have narrow therapeutic index or require rapid gastrointestinal absorption. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs at least 1 hour before Exenatide injection. . if such drugs are to be administered with food, patients should be advised to take them with a meal or snack when Exenatide is not administered.</p> <p>Drug interaction studies of exenatide have been conducted with Acetaminophen, digoxin, Lovastatin, lisinopril, oral contraceptives, warfarin.</p>	
Pregnancy and lactation	<p>Albiglutide:</p> <p>Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.</p> <p>It is not known if albiglutide is secreted into human milk during lactation. Given that albiglutide is an albumin-based protein therapeutic, it is likely to be present in human milk.</p> <p>Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation.</p>	<p>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.</p> <p>Risk communication via guidance for investigators (see albiglutide IB or</p>

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	<p>Exenatide:</p> <p>There are no adequate and well-controlled of Exenatide use in pregnant women. In animal studies, exenatide caused cleft palate, irregular skeletal ossification and an increased number of neonatal deaths.</p> <p>It is not known whether exenatide is excreted in human milk. However, exenatide is present at low concentrations in the milk of lactating.</p>	<p>exenatide PI) and informed consent form for subjects</p>
<p>Fetal & neonatal developmental toxicity [non-clinical]</p>	<p>Albiglutide</p> <p>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 (refer to Section 4.4.6 of the IB). Albiglutide is likely to be transferred to breast milk and may increase neonatal – cell mass (refer to Section 4.2.1 and Section 4.3.3 of the IB).</p> <p>Exenatide</p> <p>Based on animal data exenatide may cause fetal harm [Byetta, Prescribing Information, AstraZeneca Pharmaceuticals LP, 2015]</p>	<p>Specific eligibility and withdrawal criteria (see Section 5.1).</p> <p>Risk communication via guidance for investigators (albiglutide IB and exenatide PI) and informed consent form for subjects.</p>

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Study Design or Procedures		
EGG with water test load provokes nausea. Theoretically, vomiting may occur associated with water test load.	There are no published data on the incidence of nausea and vomiting during EGG with water load test requiring medical care. Theoretically, there is a risk of nausea or vomiting during EGG with water load test which may require medical care in this trial.	<p>Subjects will be monitored by clinical staff during EGG with water load test. The EGG water test load will be stopped at the discretion of the investigator if vomit or intense nausea or any associated AE are observed.</p> <p>Medical care in place at the investigational site to ensure patient access to any required medical treatment associated with nausea induced by test procedures</p>

AE = adverse event; ALT = alanine aminotransferase; CI = confidence interval; CV = cardiovascular; DPP-IV = dipeptidyl peptidase-IV; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1R = glucagon-like peptide-1 receptor; GSK = GlaxoSmithKline; IB = investigator's brochure; MACE = major adverse cardiovascular event; MI = myocardial infarction; MTC = medullary thyroid carcinoma; PD = pharmacodynamic; PK = pharmacokinetic; PPAR = peroxisome proliferator-activated receptor; SC = subcutaneous; T2DM = type 2 diabetes mellitus; EGG=electrogastrogram

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12.3. Appendix 3: Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM 2.0-S)

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



12.4. Appendix 4: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information

12.4.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list 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 from penile-vaginal intercourse on a long term and persistent basis. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [[Hatcher](#), 2011]
- Injectable progestogen [[Hatcher](#), 2011]
- Contraceptive vaginal ring [[Hatcher](#), 2011]
- Percutaneous contraceptive patches [[Hatcher](#), 2011]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [[Hatcher](#), 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception 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.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.4.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in [Appendix 6](#). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will discontinue study medication and be withdrawn from the study

References

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

12.5. Appendix 5: Liver Safety Required Actions and Follow up Assessments

Phase 3–4 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 3–4 liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT \geq 8xULN
ALT Increase	ALT \geq 5xULN but <8xULN persists for \geq 2 weeks ALT \geq 3xULN but <5xULN persists for \geq 4 weeks
Bilirubin^{1,2}	ALT \geq 3xULN and bilirubin \geq 2xULN (>35% direct bilirubin)
INR²	ALT \geq 3xULN and INR>1.5, if INR measured
Cannot Monitor	ALT \geq 5xULN but <8xULN and cannot be monitored weekly for \geq 2 weeks ALT \geq 3xULN but <5xULN and cannot be monitored weekly for \geq 4 weeks
Symptomatic³	ALT \geq 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> 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 SAE² 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 study treatment. If restart/rechallenge not allowed or not 	<ul style="list-style-type: none"> Viral hepatitis serology⁴ Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody⁵. Blood sample for pharmacokinetic (PK) analysis, obtained within obtained within 3 half-lives (15 days) after last dose⁶ Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). Fractionate bilirubin, if total

<p>granted, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments.</p> <p>MONITORING:</p> <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> 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 <p><u>For All other criteria:</u></p> <ul style="list-style-type: none"> 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 	<p>bilirubin\geq2xULN</p> <ul style="list-style-type: none"> 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 <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> 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.
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- Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT \geq 3xULN **and** bilirubin \geq 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
- All events of ALT \geq 3xULN **and** bilirubin \geq 2xULN (>35% direct bilirubin) or ALT \geq 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
- 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)
- Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the 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 3-4 liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
<p>ALT \geq5xULN 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.</p> <p>OR</p> <p>ALT \geq3xULN 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.</p>	<ul style="list-style-type: none"> • 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 \geq5xULN and <8xULN to \geq3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

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

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

12.6. Appendix 6: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.6.1. Definition of Adverse Events

Adverse Event Definition:

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

Events meeting AE definition include:

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

Events NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's

condition.

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

12.6.2. Definition of Serious Adverse Events

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

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

a. Results in death

b. Is life-threatening

NOTE:

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

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

<ul style="list-style-type: none"> This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: <ul style="list-style-type: none"> Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: <ul style="list-style-type: none"> ALT \geq 3xULN and total bilirubin* \geq 2xULN (>35% direct), or ALT \geq 3xULN and INR** $>$ 1.5. <p>* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT \geq 3xULN and total bilirubin \geq 2xULN, then the event is still to be reported as an SAE.</p> <p>** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.</p>

12.6.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
<p>Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs:</p> <ul style="list-style-type: none"> Myocardial infarction/unstable angina Congestive heart failure Arrhythmias Valvulopathy Pulmonary hypertension Cerebrovascular events/stroke and transient ischemic attack

- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.6.4. Recording of AEs and SAEs

AEs and SAE Recording:

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

12.6.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.7. Appendix 7: Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

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

- Response to medicine, including albiglutide and exenatide or any concomitant medicines;
- T2DM mellitus susceptibility, severity, and progression and related conditions

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

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

Study Population

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

Study Assessments and Procedures

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

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

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

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

Informed Consent

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

Subject Withdrawal from Study

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

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

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

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

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

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

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

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

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

References

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB,. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

12.8. Appendix 8 - Country Specific Requirements

No country-specific requirements exist.

12.9. Appendix 9: Protocol Changes

Protocol Amendment Number 01

Protocol Amendment Number 01 is applicable to all clinical study centers participating in this study. Protocol changes specified in Amendment Number 01 are summarized as follows:

- Part A was amended to remove the restrictions of a single-center to expand the number of participating sites to facilitate enrolment.
- Average dominant frequency was added as an exploratory endpoint for full inclusion of all EGG generated data.
- Clarification was added to the visit window for Day-1 and the options for scheduling the EGG and GEBT to allow more flexibility to assist with scheduling and therefore enrolment. In addition the dosing duration for Part A was corrected to 5 days \pm 1 day to be consistent with the visit windows in the Time and Events Table.
- Incorporated other administrative changes to update/remove duplicate terms, correct typographical errors and correct missing checks on Time and Events table.

Specific Changes in the Text: (new text is indicated by bold)

Title Page:

Author (s):

PPD [REDACTED]

Medical Monitor/Sponsor Information Page:

Role	Name	Day Time Phone Number and email address
Primary Medical Monitor	PPD [REDACTED]	PPD [REDACTED] PPD [REDACTED]

Secondary Medical Monitor	PPD	PPD PPD
SAE contact information	PPD	PPD PPD

PROTOCOL SYNOPSIS

Objectives/Endpoints Part B Objectives

Exploratory	
To evaluate change in gastric rhythm status (Data permitting)	<ul style="list-style-type: none"> At Weeks 2, 5, and 8; over 30 min and at each time interval (pre-and 10, 20 and 30 min after water load). <ul style="list-style-type: none"> Number and % of subjects with a shift in gastric rhythm status. Number and % of subjects by gastric rhythm status at each time interval. Mean and mean change from baseline in average dominant frequency

Overall Design

Part A Overall Design

- Part A is a ~~single-center~~ single arm, open label pilot phase to evaluate the effect of 5-day repeated doses of exenatide (10 µg twice daily) on GMA, GE and nausea in subjects with T2DM.
- Part A will comprise 3 study periods: screening/wash-out (up to 3 weeks), treatment (5±1 days), and post-treatment follow-up (within 7 days after the last dose of exenatide).

Part A Treatment Arms and Duration

- Part A is a single arm. All subjects will receive 10 µg subcutaneous exenatide twice daily for 5±1 days. The total duration of a subject's participation will be approximately 5 weeks.

PROTOCOL**Section 3.1 Part A: Objectives and Endpoints**

Objectives	Endpoints
Exploratory	
To evaluate change in gastric rhythm status (Data permitting)	<ul style="list-style-type: none"> • At Weeks 2, 5, and 8; over 30 min and at each time interval (pre-and 10, 20 and 30 min after water load). <ul style="list-style-type: none"> • Number and % of subjects with a shift in gastric rhythm status. • Number and % of subjects by gastric rhythm status at each time interval. • Mean and mean change from baseline in average dominant frequency

Section 3.2 Part B: Objectives and Endpoints

Objectives	Endpoints
Exploratory	
To evaluate change in gastric rhythm status (Data permitting)	<ul style="list-style-type: none"> • At Weeks 2, 5, and 8; over 30 min and at each time interval (pre-and 10, 20 and 30 min after water load). <ul style="list-style-type: none"> • Number and % of subjects with a shift in gastric rhythm status. • Number and % of subjects by gastric rhythm status at each time interval. • Mean and mean change from baseline in average dominant frequency

Section 4.1.1 Part A Overall Design

- Part A is a ~~single-center~~ single arm, open label pilot phase to evaluate the effect of 5-day repeated doses of exenatide (10 µg twice daily) on GMA, GE and nausea in subjects with T2DM
- Part A will comprise 3 study periods (Figure 1.): screening/wash-out (up to 3 weeks), treatment (5±1 days), and post-treatment follow-up (within 7 days after the last dose of exenatide).

Section 4.1.2 Treatment Arms and Duration

Part A is a single arm design. All subjects will receive 10 µg subcutaneous exenatide twice daily for 5±1 days. The total duration of a subject's participation will be approximately 5 weeks.

Section 4.6.2 Benefit Assessment

In Part A, eligible subjects will only receive exenatide for 5±1 days; the benefit in glycemic control is expected to be minimal due to this short period of treatment.

Section 6.1 Investigational Product and Other Study Treatments Table 1 Dosing Instructions.

Study Part A: 10 µg twice daily for 5±1 days

Section 6.2 Treatment Assignment

All subjects in Part A of the study will receive 10 µg exenatide twice daily for 5±1 days.

Section 6.9 Treatment after the End of the Study

In Part A, the last dose of exenatide will be in the morning before the GEBT on Day 5±1.

Section 7.1 Time and Events Table

Time and Events Table Study Part A

Procedures	Screening/Wash-Out Period (0-3 Weeks)			Treatment Period (exenatide) (5 Days)				
	Day -21 to -4	Day -3 to -5	Day -1 ¹³	Day 1	Day 2	Day 3	Day 4 ± 1 day ¹³	Day 5 ± 1 day ¹³

- For subjects taking OAM at screening only. **At a minimum**, two day washout for immediate release and **at minimum** 4 day washout for extended release OAMs. **See footnote 13.** For information on restarting OAM refer to Section 6.9

13 Every effort should be made to schedule the procedures on the nominal visit day identified. However, in order to meet scheduling needs, subjects taking OAM can schedule Day-1 up to 3 days prior to Day 1 and the OAM stopped at least the day before the GEBT . For subjects treated with diet and exercise alone Day-1 can occur within 7 days prior to Day 1. The EGG and GEBT should not be scheduled on the same day.

Table 3 Time and Events Table Study Part B (only amended rows are shown)

Procedures	Screening/Wash-Out Period (0-3 weeks)			Treatment Period (exenatide or albiglutide) (8 weeks)										Un scheduled	Early Withdrawal	Follow-Up
Study Week	-3 to -1	-1 ¹⁶		1	2 ¹⁶	3	4	5 ¹⁶			6	7	8 ¹⁶			12
Study Day	-21 to -4	-3 to -5	-1	1	10±1	-	-	29±1	31±1	32±1	-	-	52±1	53±1		78-84±3
Study Visits	1		2	3	4			5	6	7			8	9		10
OAM washout ²		X														
Height, Weight, BMI	X												X ⁶		X ⁵⁶	
FPG	X		X	X	X			X	X	X			X	X	X	
capillary blood glucose at clinic			X	X	X			X	X	X			X	X	X	X

2. For subjects taking OAM at screening only. **At a minimum**, two day washout for immediate release and **at minimum** 4 day washout for extended release OAMs. **See footnote 16.** For information on restarting OAM refer to Section 6.9

16 Every effort should be made to schedule the procedures on the nominal visit day identified. However, in order to meet scheduling needs, subjects taking OAM can schedule Day-1 up to 3 days prior to Day 1 and the OAM stopped at least the day before the GEBT. For subjects treated with diet and exercise alone Day-1 can occur within 7 days prior to Day 1. The EGG and GEBT should not be scheduled on the same day.

Section 7.3 EGG and GEBT

GEBT and EGG measurements will be undertaken in the clinic **and performed on separate days**. Measurements for both Part A and Part B will be taken at the time points specified in the Time and Events Table in Section 7.1. Clinical visits for EGG and GEBT will have a visit window of ± 1 day. ~~At the Week 5 and 8 visits, the EGG must be performed the day before the GEBT and should be planned to avoid days of expected holidays, weekends and vacations.~~

Section 7.4.10 Hyperglycemic Events

Subjects will be asked to report **any** hyperglycemic events, including **time between study visits that occur between study visits**. Subjects requiring rescue therapy due to fasting plasma glucose ≥ 270 mg/dL confirmed by central lab will be withdrawn from the study. At investigator discretion, a subject may be withdrawn for hyperglycemia at any time for safety considerations, not necessarily reaching the threshold of fasting plasma glucose ≥ 270 mg/dL

Section 9.2.4.3 Exploratory Analysis

The mean and mean change from baseline in average dominate frequency will be summarized using descriptive statistics.

Other administrative changes

- The reference to the Study Procedures Manual (SPM) was amended to Study Reference Manual (SRM) in the following Sections:
 - Section 6.6 Preparation/Handling/Storage/Accountability
 - Section 7.3.1 EGG
 - Section 7.3.2 GEBT
 - Section 7.4 Safety
 - Section 7.4.6 Gastroparesis Cardinal Symptom Index Daily Diary(GCSI-DD)
 - Section 7.4.7 Clinical Safety Laboratory Assessments
 - Section 7.6 Immunogenicity
 - Appendix 1 Abbreviations and Trademarks
 - Appendix 5 Liver Safety Required Actions and Follow-up Assessments
- Section 7.4.1 Protocol Required Laboratory Assessments

Table 4: deletion of Urea (already captured as BUN)