TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	Study 201840: An Exploratory Randomized, 2-Part, Single-blind, 2-Period Crossover Study Comparing the Effect of Albiglutide with Exenatide on Regional Brain Activity Related to Nausea in Healthy Volunteers

Compound Number: GSK716155

Development Phase: IV

Effective Date: 28-NOV-2016

Protocol Amendment Number: 1

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N250344_00	2015- MAR-28	Original
2015N250344_01	2016-MAR-30	Republished
2015N250344_02	2016-NOV-28	Amendment No. 1

Changes reflected in Protocol Amendment No. 1 have been included to address the following:

- Correct inclusion criterion #4 to MSSQ-short and a score of >17
- Correct exclusion criterion #4 to allow MRI safe glasses
- Update the exploratory endpoint GMA to adapt to the format delivered by the electrogastrographic output used during fMRI
- Clarify time period for scheduling screening procedures
- Include statement to allow rescreening with approval from Medical Monitor
- Clarify time of prohibition of food and drink to align with IRB requirements
- Incorporate administrative changes updating primary and secondary medical monitor roles

SPONSOR SIGNATORY

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Regulatory Agency Identifying Number(s):

IND Number: 065177

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 2015N250344_02

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

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

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

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201840

Rationale

Albiglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonist (Tmax 3-5 days) that has been developed as a once weekly subcutaneous injection treatment of type 2 diabetes mellitus (T2DM) and approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and other regulatory agencies. In clinical trials, nausea is a common side effect of the currently marketed GLP-1R agonists. It is not clear whether nausea associated with GLP-1R agonists is caused by stimulation of GLP-1R in the gastrointestinal system, by activation of the nausea centers at the central nervous system (CNS) via vagal afferent fibers, by direct activation of GLP-1R in the brain following blood–brain barrier penetration, or by combination of peripheral and central GLP-1R activation as the most likely mechanisms. Although the various GLP-1R agonists share the same receptor and basic mechanisms of action, differences in pharmacokinetic and pharmacodynamic characteristics may translate into differential clinical effects and tolerability profiles, with differences in the incidence of nausea in clinical trials. The dose- and time-dependent efficacy and safety effects of albiglutide were evaluated in a phase 2b dose ranging, open-label, active reference (exenatide) study. The study included two albiglutide 50 mg dosing regimens (biweekly and monthly). Exenatide 5 μg bid was up-titrated to 10 μg after 4 weeks consistent with the label to maximize tolerability. The change in HbA1c after 16 weeks was -0.79% and -0.55% for the 50 mg albiglutide biweekly and monthly regimens, respectively, and -0.54% for exenatide. The peak weekly incidence of nausea and/or vomiting for 50 mg albiglutide (without up-titration) was 25.7%. Exenatide 5 μg up-titrated to 10 μg resulted in a peak weekly incidence of nausea or vomiting of 29%. The peak weekly incidence of nausea alone was 25.7% for the 50 mg albiglutide regimens (without up-titration) and 22.6% for exenatide (up-titrated) after 4 weeks [GlaxoSmithKline Document Number ZC2007/00001/00].

To gain insight into the physiologic pathways leading to nausea associated with GLP-1R agonists, this study will explore the regional differences in brain activity and connectivity in healthy volunteers receiving single doses of albiglutide or exenatide, a short acting GLP-1R agonist that has been shown to cross the blood brain barrier in mice after peripheral administration [Kastin, 2003]. There are no human data of blood brain barrier penetration with albiglutide although limited transfer has been suggested in a murine model [GlaxoSmithKline Document Number 2015N232567_00]. For both drugs, brain activity will be assessed at the expected time of Cmax using functional magnetic resonance imaging (fMRI) to assess changes in blood oxygen level dependent (BOLD) signal in the resting-state BOLD, arterial spin labeling (ASL), and magnetic resonance spectroscopy (MRS). fMRI will be assessed without drug while nausea is induced observing the rotation of vertical stripes in a rotating drum to create the illusion of self motion (vection).

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To explore the effect of single dose 50 mg albiglutide compared to single dose 10 μg exenatide on regional brain activity and connectivity associated with nausea in healthy volunteers	• Resting-state BOLD signal (fMRI) • Regional cerebral blood flow (rCBF) (fMRI-ASL) • Glutamate concentration in nausea-associated brain regions (MRS) • GABA concentration in nausea-associated brain regions (MRS)
Secondary	
• To evaluate autonomic effects of single dose 50 mg albiglutide compared to single dose 10 μg exenatide • To assess safety and tolerability of single dose 50 mg albiglutide and single dose 10 μg exenatide	• Heart rate, heart rate variability, respiratory rate, ECG intervals, blood pressure, skin conductance level • Vital signs, clinical laboratory tests, adverse events, Nausea ratings scale, GI-VAS and MSAQ
Exploratory	
• To evaluate gastric myoelectrical activity (GMA) of single dose 50 mg albiglutide compared to single dose 10 μg exenatide	• GMA: description of frequency region(s) (Bradygastria, Normal, Tachygastria)

Overall Design

This is a phase IV, 2-part, 2-period crossover, single dose, randomized, single blind (blinded to both the subject and the imaging evaluators analysing the MRI data), placebo- and active-controlled study in adult healthy volunteers susceptible to motion sickness. The study is designed to evaluate if albiglutide and exenatide modulate nausea-related brain activity and connectivity as assessed by MRI. Placebo is used to enable albiglutide and exenatide to be dosed at different times relative to MRI due to differences in Tmax, while preserving single-blind.

The two parts of the study, Part A and Part B are the same in design, both consisting of a screening stage, a dosing/assessment stage, and a follow-up visit. Part A will test the acquisition parameters and scanning paradigms for Part B. Part A will initially randomize 4 subjects. Based on data review from the initial 4 subjects, an additional 4 subjects may be randomized for Part A. Reasons to enroll a second cohort include the need to modify acquisition parameters and scanning paradigms. If the modifications are substantial, a second cohort of 4 subjects will be added to Part A before progressing to Part B. Part B will randomize 20 subjects. Data from the Part A will inform progression, methods, and analysis plan for Part B.

After screening, eligible subjects will be randomized to one of the four crossover dosing/imaging sequences, shown in study design figure below, which include two dosing/imaging sessions and one washout period between them. Subjects will return for a follow-up visit post last dosing.

Session 1 and Session 2 each consist of 2 or 3 single-day out-patient visits according to the randomization schedule. There will be a 6-9 week washout period between Session 1 and Session 2.

- Day 1 (Session 1 or 2 per randomization) for an off-therapy MRI scan, consisting of resting-state fMRI, a nauseogenic task fMRI, ASL and MRS, and nausea associated assessments,
- Day 5 for a single dose of 50 mg albiglutide or albiglutide placebo, and
- Day 8 for a single dose of 10 μg exenatide or saline injection (exenatide placebo) followed by a post-dose MRI scan consisting of resting-state fMRI, ASL and MRS, and nausea associated assessments.

Note: Off-therapy MRI and post-dose MRI both include MRS, ASL, and resting state BOLD. In addition, the Off-therapy MRI will include a visual nauseogenic task fMRI (See Time and Events tables for full list of assessments during scan). *Number of subjects can be increased in Part A based on imaging evaluators' judgment in consultation with the Investigator and Sponsor after data review from 4 subjects

Treatment Arms and Duration

In either Part A or Part B, the total duration of a subject's participation is approximately 15-19 weeks, assuming up to 4 weeks for screening, 8 days each for Session 1 and Session 2, 6 to 9 weeks for washout, and a 4 weeks post last treatment follow-up.

Subjects will be randomized to one of the following treatment sequences:

Sequence	Session 1[a]			Session 2[a]		
1	Off-therapy MRI	50 mg albiglutide	placebo[c] (post-dose MRI)		placebo[b]	10 μg exenatide (post-dose MRI)
2		50 mg albiglutide	placebo[c] (post-dose MRI)	Off-therapy MRI	placebo[b]	10 μg exenatide (post-dose MRI)
3	Off-therapy MRI	placebo[b]	10 μg exenatide (post-dose MRI)		50 mg albiglutide	placebo[c] (post-dose MRI)
4		placebo[b]	10 μg exenatide (post-dose fMRI)	Off-therapy MRI	50 mg albiglutide	placebo[c] (post-dose MRI)

a. All administration will be given at fixed dose once daily by subcutaneous injection.
b. Placebo pen for albiglutide

c. Saline injection will be given as placebo for exenatide

All doses will be given in the morning. Overnight fasting is always required prior to MRI sessions (see details in Section 6.10.1). It is recommended that the MRI scan be scheduled for early in the morning at the same time of day for each subject for all MRI scanning sessions.

Type and Number of Subjects

Part A will initially randomize 4 subjects. Based on data review from the initial 4 subjects, an additional 4 subjects may be randomized for Part A. Part B will randomize 20 subjects.

Analysis

Data from Parts A and B will be pooled, as appropriate, for final analysis. For comparisons between albiglutide and exenatide, analysis of variance (ANOVA) will be used to analyze quantifiable endpoints with treatment and period as fixed effects, and subject as random effect. Pearson's and Spearman's correlation coefficients will be used to review relationships between selected quantifiable end points. A minimum of four subjects will be enrolled and analyzed in Part A (Cohort 1). Based on the results, a decision to enroll 4 additional subjects could be taken (Cohort 2). The criteria for this decision will be based on clinical (e.g., safety) and technical judgment after review of the neuroimaging data. Changes in brain activity associated with exenatide or albiglutide in imaging modalities tested will inform progression, methods, and analysis plan to Part B. For each subject adverse events will be reviewed by the Medical Monitor in both Parts A and B prior to the next subject being studied. Data analysis for Part A and Part B will be exploratory. The analysis plan for Part B will be finalized based on Part A results.

2. INTRODUCTION

2.1. Study Rationale

GLP-1R agonists (i.e., exenatide, liraglutide, albiglutide, and dulaglutide) are approved therapies for the treatment of T2DM. These agents mimic the action of endogenous GLP-1 stimulating the release of insulin in a glucose dependent manner and reducing glucagon secretion, effectively lowering fasting plasma glucose and hemoglobin A1c. The most commonly reported adverse events associated with the GLP-1R agonist class are nausea, vomiting and diarrhea. The rate of GI related events vary among the agents [Trujillo, 2015] and the mechanism is not fully understood. It is not clear whether nausea is caused by stimulation of GLP-1R in the gastrointestinal system resulting in delayed gastric emptying, or activation of the nausea centers at the central nervous system (CNS) via vagal afferent fibers, or directly via activation of GLP-1Rs in the brain following blood–brain barrier penetration, or a combination of these mechanisms. GLP-1R agonists share the same receptor and basic mechanisms of action, but there are differences in their pharmacokinetic and pharmacodynamic characteristics that appear to translate into differential tolerability profiles. This difference appears to be most noticeable between long acting and short acting GLP-1 receptor agonists [Østergaard, 2016].

Albiglutide, a long-acting GLP-1R agonist, (Tmax ~3-5 days), is an analogue of GLP-1 generated through genetic fusion of 2 tandem copies of modified human GLP-1 with 97% amino acid sequence homology to endogenous human GLP-1 fragment 7-36 linked to human albumin (molecular weight: 72,970 Daltons) [TANZEUM (albiglutide) for injection, 2015]. There are no human data of blood brain barrier penetration with albiglutide although limited drug transfer has been suggested in a murine model [GlaxoSmithKline Document Number 2015N232567_00]. Exenatide, a short acting GLP-1R agonist (Tmax ~2 h), is a synthetic 39 amino acid peptide amide that shares 53% sequence homology with human GLP-1 [Goke, 1993] and with a molecular weight or 4186.6 Daltons [BYETTA for injection, AstraZeneca 2015]. It has been shown to cross the blood brain barrier after peripheral administration in mice [Kastin, 2003]. However, there are conflicting data regarding whether circulating exenatide is able to cross the blood-brain barrier in humans [Schloegl, 2013].

The dose- and time-dependent effects on glycemic control and gastrointestinal (GI) tolerability of albiglutide were evaluated in a Phase IIb dose ranging, open-label study with exenatide as an active reference. The study included two 50 mg albiglutide regimens, biweekly and monthly dosing without up-titration. Exenatide 5 μg bid was up- titrated to 10 μg after 4 weeks consistent with the label to maximize tolerability. The change in HbA1c after 16 weeks was -0.79% and -0.55% for the 50 mg albiglutide biweekly and monthly regimens, respectively, and -0.54% for exenatide. The peak weekly incidence of nausea or vomiting for 50 mg albiglutide (biweekly or monthly dosing arms without up-titration) was 25.7%. Exenatide 5 μg up-titrated to 10 μg reported a peak weekly incidence of nausea or vomiting of 29%. The peak weekly incidence of nausea alone was 25.7% for the 50 mg albiglutide regimens (without up-titration) and 22.6% for exenatide (up-titrated) after 4 weeks [GlaxoSmithKline Document Number ZC2007/00001/00].

There continues to be an interest in the mechanism underlying the GI side effects with GLP-1R agonists [Smits, 2015]. To gain insight into the central mechanisms of nausea associated with GLP-1R agonists, this study will explore the potential differences at the expected time of C_{max} between a long-acting (albiglutide) and short-acting (exenatide) GLP-1R agonist in brain activation of healthy volunteers, with special interest on regions found in previous research to be associated with vection-induced nausea [Napadow, 2013, Farmer, 2015]. Nausea central mechanisms are complex. The brain regions associated with pharmacologic or vection-induced nausea have been studied and demonstrated some overlap in the activated regions as well as some divergences [Napadow, 2013; Miller, 1996].

The drug effects will be studied after a single dose of 50 mg albiglutide and a single dose of 10 μg exenatide using 1) functional magnetic resonance imaging (fMRI) to assess changes in resting-state blood oxygen level dependent (BOLD) signal, 2) arterial spin labeling (ASL), and 3) magnetic resonance spectroscopy (MRS). The highest approved doses will be used to maximize the potential to observe nausea and the timing of the MRI will overlap with $C_{max.}$ Due to the difference in expected time of Cmax (albiglutide 3-5 days and exenatide 2 hrs), the timing of MRI and other key study assessments relative to dosing are scheduled to coincide with expected Cmax timing. Placebo is used to maintain the single-blind.

Observing the rotation of vertical stripes in a rotating drum to create the illusion of self motion (vection) is a well characterized stimulus (task) that can serve as a map of the central response to nausea [Napadow, 2013; Farmer, 2015]. Each subject will be studied under this standardized condition without the study medication to identify the brain circuitry associated with motion sickness induced nausea (an established vection task). Group analyses will then compare brain outcomes (e.g. connectivity) for motion sickness induced nausea versus nausea induced by different drugs to allow the inference of GLP 1R agonist effects in nausea related brain activation. The group activation maps generated from the vection task scans will also be used to define ROIs to better interrogate the drug-induced alterations in other neuroimaging outcomes (i.e. ASL, MRS). Each subject will act as their own control in this crossover design. The resting-state BOLD and cerebral blood flow (rCBF-ASL) will both be used to provide insight into the connectivity of the central nausea response.

By examining BOLD signals at rest and during task, ASL-rCBF changes and assessing in vivo metabolic changes through MRS [glutamate and gamma-aminobutyric acid (GABA) concentrations], the relationship between neurotransmitter concentration and brain activation/deactivation in specific brain regions will be explored.

The information from this study is expected to be of benefit for patients in the future, as insights on the mechanisms of nausea associated with GLP 1 receptor agonists are needed to design new strategies to minimize the occurrence and impact of these AEs with drugs currently in use, and to design new drugs able to avoid these mechanisms.

2.2. Brief Background

Albiglutide has been approved in the European Union (EU), the US, and other countries for the treatment of T2DM as an adjunct to diet and exercise, as monotherapy (EU), or in combination with existing therapies. 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]; [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. 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]. Exenatide has been approved in the US indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To explore the effect of single dose 50 mg albiglutide compared to single dose 10 μg exenatide on regional brain activity and connectivity associated with nausea in healthy volunteers	• Resting-state BOLD signal (fMRI) • Regional cerebral blood flow (rCBF) (fMRI-ASL) • Glutamate concentration in nausea-associated brain regions (MRS) • GABA concentration in nausea-associated brain regions (MRS)
Secondary	
• To evaluate autonomic effects of single dose 50 mg albiglutide compared to single dose 10 μg exenatide • To assess safety and tolerability of single dose 50 mg albiglutide and single dose 10 μg exenatide	• Heart rate, heart rate variability, respiratory rate, ECG intervals, blood pressure, skin conductance level • Vital signs, clinical laboratory tests, adverse events, Nausea ratings scale, GI VAS, and MSAQ
Exploratory	
• To evaluate gastric myoelectrical activity (GMA) of single dose 50 mg albiglutide compared to single dose10 μg exenatide	• GMA: description of frequency region(s) (Bradygastria, Normal, Tachygastria)

4. STUDY DESIGN

4.1. Overall Design

This is a phase IV, 2-part, 2-period crossover, single dose, randomized, single blind (blinded to both the subject and the imaging evaluators analysing the MRI data), placebo- and active-controlled study in adult healthy volunteers who are susceptible to motion sickness. The study is designed to evaluate if albiglutide and exenatide modulate nausea-related brain activity and connectivity as assessed by MRI.

The two parts of the study, Part A and Part B are the same in design, both consisting of a screening stage, a dosing/assessment stage, and a follow-up visit. Part A will test the acquisition parameters and scanning paradigms to agree the experimental process for Part B. Data from Part A will inform progression, methods, and analysis plan for Part B. Placebo is used to enable albiglutide and exenatide to be dosed at different times relative to MRI due to differences in Tmax, while preserving single-blind. Part A will initially randomize 4 subjects. Based on data review from the initial 4 subjects, an additional 4 subjects may be randomized for Part A. Reasons to enroll a second cohort include the need to modify acquisition parameters and scanning paradigms. If the modifications are substantial, a second cohort of 4 subjects will be added to Part A before progressing to Part B. Part B will randomize 20 subjects.

After screening, eligible subjects will be randomized to one of the four crossover dosing/imaging sequences. Each sequence includes three scanning visits: albiglutide plus scan, exenatide plus scan and an off-therapy –natural history scan with a 6-9 week

washout period between the dosing scans. Subjects will return for a follow-up visit post last dosing.

Note: Off-therapy MRI and post-dose MRI both include MRS, ASL, and resting state BOLD. In addition, the Off-therapy MRI will include a visual nauseogenic task fMRI (See Time and Events tables for full list of assessments during scan). *Number of subjects can be increased in Part A based on imaging evaluator judgment in consultation with the Investigator and the Sponsor after data review from 4 subjects.

In both Part A and Part B, subjects who meet the eligibility criteria will be randomized in a crossover fashion to one of 4 different sequences, each consisting of two dosing/imaging sessions (Session 1 and Session 2) separated by a 6-9-week washout period (Section 4.2 Table 1). Each subject will undergo a single off-therapy MRI during a separate Visit according to the randomization sequence to minimize the total number of scans per subject. The timing or sequencing of the off-therapy MRI will be randomized (i.e. Session 1 or Session 2) to account for potential learning effects. Each subject will undergo one off-therapy MRI, one post-dose albiglutide MRI and one post-dose exenatide MRI for a total of 3 MRI scans during the study. The visit schedule is set to allow the Off-therapy MRI scan visit to occur approximately 7 days prior to the post-dose scan within the Session as this is the minimal recommended time between scans. The visit on Day 5 allows the dosing of albiglutide or albiglutide placebo to occur 4±1 days before the post-dose MRI i.e., at estimated T_{max} (3-5 days). Because of the short Tmax (2 hrs) for exenatide, exenatide or saline placebo is given on the day of the MRI scan (Day 8). Therefore, MRI Session 1 and Session 2 each consist of 2 or 3 single-day out-patient visits according to the randomization schedule on the following days:

- Day 1 (Either Session 1 or 2 per randomization) for an off-therapy MRI scan consisting of resting-state fMRI, a nauseogenic task fMRI, ASL and MRS and nausea associated assessments,
- Day 5 for a single dose of 50 mg albiglutide or albiglutide placebo, and
- Day 8 for a single dose of 10 μg exenatide or saline placebo followed by a post-dose MRI scan consisting of resting-state fMRI, ASL and MRS, and nausea associated assessments.

Subjects will be blindfolded when receiving the study medication injection to maintain the single-blind.

For all MRI sessions, subjects must fast overnight and will be instructed to refrain from eating and drinking anything but water starting at approximately 10 pm the night before or with in 8 hours of the start of their MRI appointment.

For the off-therapy session, MRI scan and nausea associated assessments will be conducted without prior injection (no drug, no placebo).

On post-dose scanning visits, subjects will be offered a meal after the procedure before leaving the unit, and capillary glycemia will be assessed.

The Investigator or medically qualified site staff will approve the release of the subject from the clinic or will provide treatment as per standard of care as required.

Subjects in either Part A or Part B will have a total of 8 planned visits: Screening, mock MRI, Session 1 or 2 off therapy MRI, Session 1 Day 5 dosing, Session 1 Day 8 dosing and post-dose MRI, Session 2 Day 5 dosing, Session 2 Day 8 dosing and post-dose MRI, and Follow-up (see Section 7.1 Time and Events table).

Part A data review

Safety data from each subject enrolled in Part A will be reviewed in stream by the study team, and imaging data will be pre-processed and assessed for quality in stream. Once the first 4 subjects enrolled in Part A have completed, data will be reviewed. The evaluation will include safety of exenatide and albiglutide administration at stated doses during MRI, fidelity of imaging and physiological (e.g. EGG) measures taken during the different MRI scan sessions. Outcome options may include modifying acquisition parameters and the scanning paradigm. If the modifications are substantial a second cohort of 4 subjects may be added to Part A before progressing to Part B. The decision to either modify the imaging paradigms, randomize 4 more subjects for Part A or progress to Part B will be made based on the imaging evaluator's judgment in consultation with the PI and Sponsor. A second interim data review will occur only if a decision to randomize 4 more for Part A is made after initial review of results from the first 4 subjects. This second review, should it occur, will use all data from 8 subjects. Adjustments to the study design of Part B (e.g., endpoint evaluation) may be made prior to progression to Part B.

Part A data review is part of the exploratory nature of this study and could result in refinement of endpoints and statistical analysis. These changes will be documented in the RAP and will not be considered an amendment to the Protocol.

4.2. Treatment Arms and Duration

Table 1 Randomization Sequences for Part A and Part B

Sequence	Session 1[a]			Session 2[a]		
1	Off-therapy MRI	50 mg albiglutide	placebo[c] (post-dose MRI		placebo[b]	10 μg exenatide (post-dose MRI
2		50 mg albiglutide	placebo[c] (post-dose MRI	Off-therapy MRI	placebo[b]	10 μg exenatide (post-dose MRI
3	Off-therapy MRI	placebo[b]	10 μg exenatide (post-dose MRI		50 mg albiglutide	placebo[c] (post-dose MRI
4		placebo[b]	10 μg exenatide (post-dose MRI	Off-therapy MRI	50 mg albiglutide	placebo[c] (post-dose MRI

a. All administration will be given at fixed dose once daily by subcutaneous injection.
b. Placebo pen for albiglutide
c. Saline injection will be given as placebo for exenatide

All doses will be given in the morning. For all MRI sessions subjects must fast overnight and will be required to refrain from eating and drinking anything but water starting at approximately 10 pm the night before or with in 8 hours of the start of their MRI appointment (see Section 6.10.1). It is recommended that the MRI scan be scheduled for early in the morning at the same time of day for each subject for all MRI Sessions.

4.3. Type and Number of Subjects

This study will enrol both male and female healthy volunteers 18-50 years old who are right handed and sensitive to motion sickness. Approximately 60 healthy adults will be screened to achieve a total (from Parts A and B) of 24 or 28 randomized subjects.

In Part A, approximately 10 healthy adults will be screened to achieve 4 randomized. An additional 4 subjects (Cohort 2) may be randomized if changes to the acquisition parameters and scanning paradigm require confirmation before progressing to Part B.

If subjects prematurely discontinue the study or individual subject technical issues arise, subjects may be replaced at the discretion of the Investigator or imaging evaluators in consultation with the Sponsor. Subjects will be assigned to the same treatment sequence in order to meet the target number of subjects.

4.4. Design Justification

This exploratory study is designed to gain insight into a potential central 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. Healthy volunteers will be enrolled in this study to allow an evaluation without the interference of morbidity. Single dose provides evidence of initial brain response to drug stimuli avoiding unnecessary exposure of healthy volunteers to the drugs being investigated. The crossover design is preferred because it allows the subject to act as their own control in the assessment of nausea which has a very strong subjective component [Levine, 2005]. Including subjects susceptible to motion sickness may

improve baseline nauseogenic central response. The assessment of CNS regional activation to nauseogenic drugs using fMRI comparing with standardized nauseogenic stimulus based on motion sickness is untested. Therefore, the study will be implemented in two parts. Part A will attempt to characterize brain activation with drug in comparison with brain activation with task identifying magnitude of signals, noise, artefacts, tolerability and safety. Data from Part A will be analyzed to identify adjustments needed to the imaging technique to progress to the main study, Part B.

fMRI is non-invasive and widely available modality to measure drug effects on brain function. [Wang, 2010; Duncan, 2014]. fMRI has been used to characterize nausea induced by perception of movement (motion sickness model). This study will combine the knowledge of pharmacological intervention and standardized task to study nausea, aiming to provide insight on drug effect in known patterns of brain activation and connectivity associated with nausea. Resting-state fMRI will measure BOLD signal to identify neuronal activity and relevant networks with and without study medication. fMR imaging during visual nauseogenic task will assess the percent change in BOLD without study medication to identify the activation of brain regions associated with nausea. In addition to the hemodynamic changes as measured by BOLD signal and ASL, the study will investigate the correlation of chemical changes in two neurotransmitters, GABA and glutamate via MRS.

This exploratory study will include exenatide, a well-studied short-acting GLP-1 receptor agonist, as the active control. Exenatide has been shown to induce nausea at an incidence of 61.7% after a single 10 μg dose in healthy volunteers over 24 hrs post-dose [Ellero, 2010]. Temporal changes in the fMRI BOLD signal were observed after a single 5 μg dose of exenatide [McKie, 2013]. The timing of the MRI is chosen to coincide with albiglutide and active control expected Tmax. Therefore, the MRI is planned in 3 days for albiglutide but conducted after 1 hr for exenatide. The washout period between injections is 6-9 weeks due to the long half-life of albiglutide (T1/2= 5 days). Six to nine weeks will allow the scheduling of the scan visits to be aligned with the same phase of the menstrual cycle, when possible, for women of reproductive age.

This exploratory study includes placebo (albiglutide placebo or saline subcutaneous injection) to maintain the subject's blind and account for potential central activation that may result from receiving an injection prior to the MRI scan.

4.5. Dose Justification

To maximize an observed effect of nausea, the dose of albiglutide in this study is 50 mg, the highest approved clinical dose for treatment of adults with T2DM. To date, single doses of up to 100 mg have been safely administered to healthy volunteers in clinical trials [IB].

The highest approved clinical dose of 10 μg exenatide will be used as the active control. This dose has been safely used in clinical trials in healthy volunteers. A single subcutaneous dose (10 μg) of exenatide was administered to 120 healthy subjects. Among all subjects, mild to moderate nausea was the most frequent adverse event after exenatide dosing. Vomiting was also observed. [Ellero, 2010].

4.6. Benefit:Risk Assessment

Albiglutide has been evaluated in a comprehensive global program of studies. Sixty-two healthy volunteers have been exposed to one or two doses of albiglutide and 190 healthy volunteers have been exposed to multiple doses of albiglutide. In the Phase III program, approximately 9000 patient-years of overall exposure to date (including over 4000 patient-years of exposure to albiglutide), with 8 well-controlled studies (including 1 study in subjects with concurrent renal impairment), ranging in duration from 32 weeks to 3 years and using both 30 mg and 50 mg once-weekly dosing. This has permitted a robust assessment of efficacy, safety, and tolerability in a representative T2DM population. Across all studies, albiglutide was generally safe and well-tolerated.

Summaries of findings from both clinical and nonclinical studies conducted with albiglutide can be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number RM2006/00602/08; and Supplement 1 GlaxoSmithKline Document Number 2015N256204_00] and the product label [TANZEUM (albiglutide) for injection, 2015]. The following section outlines the risk assessment and mitigation strategy for this protocol.

There is no expected health benefit to individual healthy volunteers participating in the study. Risks of study medications and procedures are communicated to participating subjects via the Informed Consent document. Additionally investigators are informed about risks via the US Prescribing Information and the Investigator Brochure. The information from this study is expected to be of benefit for patients in the future, as insights on the mechanisms of nausea associated with GLP 1 receptor agonists are needed to design new strategies to minimize the occurrence and impact of these AEs with GLP 1 receptor agonist drugs currently in use, and to design new drugs able to avoid these mechanisms.

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product: (albiglutide (GSK716155) and exenatide (Byetta)) Identified Risks		
Pancreatitis	Albiglutide: In clinical trials, acute pancreatitis has been reported in association with albiglutide and other GLP-1R agonists (refer to Section 5.4. and Section 6 of the IB). Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether these subjects are at increased risk for pancreatitis. Exenatide: Based on post marketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis (Byetta, Prescribing Information, AstraZeneca Pharmaceuticals LP, 2015). Exenatide has not been studied in subjects with a history of pancreatitis.	Specific eligibility and withdrawal criteria (see Section 5.2 and Section 5.4) Risk communication via guidance for investigators (albiglutide IB and Prescribing Information (PI) and exenatide PI) and informed consent form for subjects
Gastrointestinal (GI) events	Albiglutide: Albiglutide has not been studied in subjects with severe GI disease, including severe gastroparesis. Use of albiglutide may be associated with GI AEs (e.g., diarrhea, nausea, and vomiting) (refer to Section 5.4.and Section 6 of the IB). Exenatide: Exenatide has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because exenatide is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting and diarrhea, the use of exenatide is not recommended in patients with severe gastrointestinal disease (Prescribing Information, AstraZeneca Pharmaceuticals LP, 2015)	Specific GI eligibility and withdrawal criteria (see Section 5.2 and Section 5.4) Risk communication via guidance for investigators (albiglutide IB and PI and exenatide PI) and informed consent form for subjects
Hypoglycemia	Albiglutide Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycemia (refer to Section 5.4. and Section 6 of the IB). Exenatide	The risk of hypoglycemia in this study is anticipated to be low as study medications will be single-dose and in healthy volunteers. Subjects will receive a meal after the imaging session. Investigator or medically qualifies

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	The risk of hypoglycemia is increased when exenatide is used in combination with medications known to cause hypoglycemia (e.g., insulin and insulin secretagogue) (Byetta, Prescribing Information, AstraZeneca Pharmaceuticals LP, 2015).	staff will approve the discharge of subjects after IP administration and/or imaging session. Post-scan measure of capillary blood glucose and withdrawal criteria (see Section 5.4) Risk communication via guidance for investigators (albiglutide IB and PI and exenatide PI) and informed consent form for subjects
Immunogenicity (e.g., clinical sequelae of antidrug antibodies,)	Albiglutide In the Phase III 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 (refer to Section 5.6. of the IB). 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%). Exenatide: Patients may develop antibodies to exenatide following treatment In 1-4% of the subjects measured for antibody formation in clinical trials, formation of antibodies was associated with attenuated glycemic control. (Byetta, Prescribing Information, AstraZeneca Pharmaceuticals LP, 2015).	Specific eligibility and withdrawal criteria (see Section 5.2 and Section 5.4) Risk communication via guidance for investigators (albiglutide IB and PI and exenatide PI) and informed consent form for subjects
Hypersensitivity reactions	Albiglutide: Hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III program (refer to Section 5.4 and Section 6 of the IB). Across 8 Phase III clinical trials, a serious hypersensitivity reaction with pruritus, rash, and dyspnea occurred in a patient treated with albiglutide. Exenatide: There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis	Specific eligibility and withdrawal criteria (see Section 5.2 and Section 5.4) Risk communication via guidance for investigators (albiglutide IB and PI and exenatide PI) and informed consent form for subjects

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and angioedema) in patients treated with exenatide (Byetta, Prescribing Information, AstraZeneca Pharmaceuticals, 2015).	
Injection site reactions	Albiglutide: 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 (IB Section 5.4). Exenatide: Injection-site reactions have been reported during post approval use of exenatide (Byetta, Prescribing Information, AstraZeneca Pharmaceuticals LP, 2015).	Risk communication via guidance for investigators (albiglutide IB and PI and exenatide PI) and informed consent form for subjects
Other adverse reactions	Albiglutide: In the Phase III program, other adverse reactions (e.g., pneumonia, atrial fibrillation/atrial flutter, and appendicitis) were observed with a cumulative incidence of <3% in studies up to 3 years in duration (Refer to Section 5.4 and Section 6 of the IB). Exenatide: The following additional adverse reactions have been reported during post approval use of exenatide: dysgeusia; somnolence, and alopecia Increases in international normalized ratio with concomitant use of warfarin sometimes associated with bleeding. Renal impairment sometimes requiring hemodialysis and kidney transplant (Byetta, Prescribing Information, AstraZeneca Pharmaceuticals LP, 2015).	Risk communication via guidance for investigators (albiglutide IB Section 6 and exenatide PI) and informed consent form for subjects
Thyroid C-cell tumors	Albiglutide: 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. In Phase III studies of up to 3 years in duration, albiglutide was not associated with clinically relevant increases in serum calcitonin (refer to Section 5.4 and Section 6 of the IB).	Specific eligibility criteria (see Section 5.2). Risk communication via guidance for investigators (albiglutide IB and PI and exenatide PI) and informed consent form for subjects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Exenatide A 104-week carcinogenicity study was conducted in male and female rats at doses of 18, 70 or 250 mcg/kg/day administrated by bolus SC injection, benign thyroid C-cell adenomas were observed in female rats at all exenatide doses.	
Pancreatic cancer	Theoretical concern for pancreatic cancer associated with GLP-1-based therapies (Dipeptidyl peptidase (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.	Eligibility and withdrawal criteria (see Section 5.2 and Section 5.4)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hepatotoxicity	Albiglutide: One subject in the Phase III 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 (refer to Section 5.4 of the IB).	Specific eligibility and withdrawal criteria (see Section 5.2 and Section 5.4)
Drug interactions	Albiglutide: Albiglutide causes a delay in gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications (refer to Section 5.2 and Section 6 of the IB). Drug interaction studies have been conducted with digoxin, warfarin, oral contraceptives, and simvastatin, which demonstrated no clinically relevant PK or PD effects. Exenatide: 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 injectionif 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. Drug interaction studies of exenatide have been conducted with acetaminophen, digoxin, lovastatin, lisinopril, oral contraceptives, warfarin (Byetta, Prescribing Information, AstraZeneca Pharmaceuticals LP, 2015).	This study is being conducted on HV and we do not expect they will be taking concomitant medications. Risk communication via guidance for investigators (albiglutide IB and PI and exenatide PI).
Pregnancy and lactation	Albiglutide: Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown (refer to Section 4.4 and Section 6 of the IB). It is not known if albiglutide is secreted into human milk during lactation. Given that albiglutide is an albumin-based protein therapeutic, it is likely to be present in human milk. Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation.	Specific eligibility and withdrawal criteria (see Section 5.2 and Section 5.4) Only a single dose of albiglutide (50 mg) and single dose of exenatide (10 µg) will be administered per subject. Risk communication via guidance for investigators (albiglutide IB and PI and exenatide PI) and informed consent form for

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Exenatide: 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. It is not known whether exenatide is excreted in human milk. However, exenatide is present at low concentrations in the milk of lactating mice (Byetta, Prescribing Information, AstraZeneca Pharmaceuticals LP, 2015).	subjects
Study Procedures		
Nausea and or vomiting during visual nauseogenic task	Vection has been found to be a reliable method to study nausea (associated with motion) in combination with functional neuroimaging [Farmer, 2015]. Vection induces nausea and can possibly induce vomit.	Risk communication via informed consent form for subjects. • Subjects will be fasting overnight prior to each scanning session. • Training of subjects on reporting nausea during fMRI sessions and nausea rating in mock fMRI. • Instructing subjects how to stop nauseogenic stimulation if the subject feels the urge to vomit during fMRI sessions, in order to avoid vomit • Medical care with trained site staff to treat nausea and or vomit and provide medical support for emergencies.
MRI	Magnetic resonance imaging (MRI) is a medical imaging procedure that uses strong magnetic fields and radio waves to produce cross-sectional images of organs and internal structures in the body. Therefore ferromagnetic interactions with devices, implants or other metallic items may occur. Patients with severe claustrophobia may not be able to tolerate an MRI scan	Specific eligibility and withdrawal criteria (see Section 5.2 and Section 5.4) Subjects will undergo a “MOCK fMRI’ session to evaluate tolerability of placement in scanner

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other (Albiglutide/exenatide matching placebos)		
Albiglutide matching placebo injections	Albiglutide placebo s.c. injections were associated with a clinically relevant rate of injection site reactions (Refer to Section 5.4.5.6 of the IB).	Risk communication via informed consent form for subjects. Only a single s.c. dose of placebo will be administered per subject.
Saline injections	Exenatide placebo (saline) risk of injection site reaction with saline is unknown, and thought to be low risk.	Risk communication via informed consent form for subjects. Only a single s.c. dose of placebo will be administered per subject.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the albiglutide or exenatide that may impact subject eligibility is provided in the albiglutide IB [GlaxoSmithKline Document Number GlaxoSmithKline Document Number RM2006/00602/08; Supplement 1 GlaxoSmithKline Document Number 2015N256204_00] and the product label [TANZEUM (albiglutide) for injection, GlaxoSmithKline 2015] and in the BYETTA (exenatide) product insert [BYETTA for injection, AstraZeneca 2015].

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, 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 50 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy as determined by the Investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
3. Pure right-handed based on Edinburgh Handedness Inventory (Appendix 5)
4. Motion Sickness Susceptibility Questionnaire (MSSQ-short) Screening score >17 and mock fMRI nausea rating ≥2(See Appendix 6)
5. 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 may be included only if 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.

WEIGHT
6. Subject's body mass index (BMI) is ≥19 kg/m^2 and ≤30kg/m^2.

SEX

7. Male OR
8. Female: eligible to participate if she is not pregnant (as confirmed by a negative human chorionic gonadotrophin (hCG) test at screening and at other timepoints), not lactating, and at least one of the following conditions applies:
   - Non-reproductive potential defined as:
     - Pre-menopausal females with one of the following:
       - Documented tubal ligation
       - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
       - Hysterectomy
       - Documented Bilateral Oophorectomy
     - Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause to confirm (refer to laboratory reference ranges for confirmatory levels)].
   - Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and for the duration of study including the completion of the follow-up visit.

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. 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 sterilisation 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.

INFORMED CONSENT
9. 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. Severe nausea (with or without vomiting) in the last three months or any event of unexplained nausea (with or without vomiting) as reported by the subject in the last 14 days before screening.
2. History of vestibular or balance disorders as determined by the Investigator.
3. History of smoking cigarettes or using tobacco products or any nicotine-containing products (including nicotine patches) within 3 months of screening.
4. Subjects requiring visual correction to participate in visual task that cannot be corrected with contact lenses or MRI safe glasses.
5. ALT >1.5xULN
6. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
7. Current or chronic history of liver disease, or known hepatic or biliary abnormalities
8. QTcF > 450 msec, where QTcF is the QT interval corrected for heart rate according to Fridericia's formula
9. Systolic blood pressure is ≥140 mm Hg at Screening; repeat blood pressures should be taken if the subject's systolic blood pressure is ≥140 mm Hg and if the results are consistently ≥140 mm Hg, then the subject should be excluded and advised to consult a physician
10. Diastolic blood pressure is ≥ 90 mm Hg at Screening; repeat blood pressures should be taken if the subject's diastolic blood pressure is ≥ 90 mm Hg and if the results are consistently ≥ 90 mm Hg, then the subject should be excluded and advised to consult a physician
11. Mean resting heart rate is >100 beats/min out of 3 consecutive measures taken 10 minutes apart at Screening
12. History of intestinal obstruction, ileus, gastrointestinal surgery or any other medical condition or procedure (e.g., gastrectomy, gastric bypass, lap-band) that may impair gastrointestinal motility

13. History of significant cardiovascular or pulmonary dysfunction prior to screening
14. History of acute or chronic pancreatitis
15. History of severe gastrointestinal disease, including gastroparesis, inflammatory bowel disease, Crohn's disease, or irritable bowel syndrome
16. History of any significant psychiatric illness (e.g., schizophrenia, bipolar affective disorder, bulimia or anorexia nervosa) that in the opinion of the Investigator would interfere with participation in the study.
17. History and/or evidence of any other CNS disorder that in the opinion of the Investigator would interfere with participation in the study (e.g., epilepsy, brain tumour, brain surgery).
18. History of clinically significant CNS trauma (e.g. traumatic brain injury, cerebral contusion, spinal cord compression) or seizures.

CONCOMITANT MEDICATIONS

19. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.
20. Received within 7 days prior to screening or unable to refrain from taking for the duration of each part of study, medications that might
    - modify gastric myoelectical activity or gastrointestinal motility as prokinetic (e.g., erythromycin), anti-emetic agents (e.g., metoclopromide), narcotic analgesics (e.g., morphine), anticholinergic drugs(e.g., domperidone), anti-acid (e.g., pump inhibitors, H2 blockers) and laxative agents
    - stimulate or inhibit CNS (e.g., modafinil, dexamphetamine, methylphenidate, bromopheniramine, chlorpheniramine, clemastine, diphenhydramine, hyrdoxyzine)

RELEVANT HABITS

21. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.
22. Is unwilling to abstain from alcohol for 24 hours before dosing and before each MRI scanning visit
23. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 3 months prior to screening.
24. Subject has a history of significant weight loss (>5% reported change within 3 months prior to screening) or is currently attempting weight loss

CONTRAINDICATIONS
25. History of hypersensitivity to albiglutide, exenatide, or any product components
26. Personal or family history of multiple endocrine neoplasia type 2, or medullary carcinoma of the thyroid
27. Subject has any known condition(s) that may be contraindicated or interfere with the completion of MRI scanning such as implants (e.g., pacemaker, cochlear), a medical or electronic device (e.g., metallic joint prostheses, metal pins, screws, plates, stents or surgical staples), or claustrophobia.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
28. An abnormal (i.e., outside the normal reference range) thyroid function test assessed by thyroid stimulating hormone and Free T4 at screening.
29. An abnormal amylase or lipase test at screening
30. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening or at screening
31. A positive pre-study drug/alcohol screen
32. A positive test for human immunodeficiency virus (HIV) antibody
33. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56-day period
34. Subject has previously received any GLP-1R agonist at any time (e.g., albiglutide, exenatide, liraglutide, lixisenatide, dulaglutide)
35. Subject has previously received DPP-IV inhibitor (sitagliptin, saxagliptin, linagliptin, alogliptin) within 30 days from screening
36. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
37. Exposure to more than 4 new investigational products within 12 months prior to the first dosing day.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events. Subjects can be rescreened once if agreed after discussion with the Medical Monitor.

5.4. Withdrawal/Stopping Criteria

A subject may withdraw from the study at any time at his or her own request, or may be withdrawn at any time at the discretion of the Investigator or the Sponsor for safety, behavioral, or administrative reasons. Safety data will be reviewed by the Sponsor in-stream by single case and collectively. If a safety concerns arises, a decision about continuation of the study will be made.

Any subject presenting with nausea symptoms on the day of the off-therapy MRI or who had vomited within 12 hours prior to the scheduled off-therapy MRI session visit can be rescheduled for the visit or withdrawn at the Investigator's discretion.

Subjects who cannot complete any of the study procedures may be replaced at the discretion of the Investigator after consultation with the Sponsor.

A subject MUST be withdrawn from the study for the reasons including, but not limited to:

- 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
  - Pancreatic cancer.
  - Confirmed MTC or other thyroid C-cell neoplasia.
  - Liver chemistry abnormalities exceeding the threshold criteria outlined in Appendix 2
  - Severe allergic/hypersensitivity reactions that are considered by the Investigator to be attributable to investigational product or without a likely alternative aetiology.
  - QTc stopping criteria (see Section 5.4.2)
  - AE, which, in the opinion of the Investigator, requires withdrawal
  - Severe hypoglycemia, which, in the opinion of the Investigator or medical monitor, requires withdrawal
- Consent withdrawn
- Lost to follow-up
- Termination of study by sponsor
- Pregnancy
- Any untoward findings during the MRI scan that may jeopardize the imaging analysis or subject safety.

A subject MAY be withdrawn from the study for the reasons including, but not limited to:

- Nausea or vomiting requiring the use of anti-emetics or other interventions
- Protocol deviation (the Investigator should discuss the protocol deviation with the medical monitor before withdrawing a subject)
- Noncompliance with study visit schedule, as determined by the Investigator in consultation with the sponsor
- Other: the reason must be documented on the electronic Case Report Form (eCRF)

5.4.1. Liver Chemistry Stopping Criteria

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

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.2. QTc Stopping Criteria

A subject that meets either bulleted criterion below will be withdrawn from the study.

- QTcF >500 msec,
- Change from baseline: QTcF >60 msec

5.4.3. Withdrawal Procedures

Subjects who withdraw from the study before completion of all procedures and assessments must complete all assessments for the follow-up visit (see Time and Events Table, Section 7.1).

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

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed ‘lost to follow up’, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record.

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

5.5. Subject and Study Completion

A completed subject is one who has completed all scheduled visits including follow-up.

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.

	Study Treatment			
Product name:	**Albiglutide (GSK716155)**	**Matching albiglutide placebo**	**Exenatide (Byetta)**	**Exenatide placebo (saline)**
Formulation description:	Single-use fixed dose, fully disposable pen injector system for SC delivery	Single-use fixed dose, fully disposable pen injector system for SC delivery	A sterile solution containing 250 μg /mL exenatide	Sterile saline
Dosage form:	50 mg pen: Contains 67 mg lyophilised albiglutide and 0.65 mL diluent designed to deliver a dose of 50 mg in a volume of 0.5 mL after reconstitution.	NA	10 μg per dose in 2.4 mL prefilled pen. One dose will be used.	NA
Unit dose strength(s)/Dosage level(s):	50 mg in 0.5 mL injector volume	0.5 mL injector volume	10 μg per dose in 2.4 mL prefilled pen	0.04 mL
Route of Administration	SC	SC	SC	SC

	Study Treatment			
Dosing instructions:	To be reconstituted as directed in the SRM. Inject SC in the upper arm.	To be reconstituted as directed in the SRM. Inject SC in the upper arm.	Follow new pen set-up in prescribing information. Inject SC in the upper arm.	Inject SC in the upper arm.

6.2. Treatment Assignment

Randomized treatment assignment will be done via web-based interactive response (IRT) system (RAMOS NG).

Subjects will be randomized to one of the 4 crossover dosing/imaging sequences in either Part A or Part B. Once the required number of subjects have been randomized e.g. Cohort 1 in Part A, randomization of additional subjects will be put on hold. Randomization will resume after decision to either enroll a second Cohort in Part A or progress to Part B has been made.

Site personnel will receive a randomization notification indicating the unique subject identifier, the treatment sequence, 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 randomized study medication.

6.3. Planned Dose Adjustments

There are no planned dose adjustments in this study.

6.4. Blinding

This will be a single blind (GSK and site staff are unblinded but subjects and imaging evaluators of MRI are blinded) study and the following will apply. Evaluators in this study are staff who analyze neuroimaging data. Every attempt will be made to maintain the single-blind. Exenatide placebo is not available for this study. An injection of saline using the same needle size will be given to the subjects who will be blind-folded at the time they receive the injection.

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

- 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.

Albiglutide and matching albiglutide placebo

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

Exenatide and placebo (saline)

A description of the methods and materials required for dosing of exenatide is provided in the SRM.

Sterile saline s.c. as the exenatide placebo will be administered and will be detailed in the SRM.

Exenatide s.c. injection or placebo of exenatide s.c injection will be administered by the site staff.

6.7. Compliance with Study Treatment Administration

Subjects are dosed at the site, and 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. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.8. Treatment of Study Treatment Overdose

In the event of an overdose the Investigator should:

1. contact the Medical Monitor immediately
2. closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until albiglutide or exenatide can no longer be detected systemically (at least 25 days for albiglutide or 24 hrs for exenatide).
3. document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.8.1. Albiglutide

For this study, once the 50 mg dose of albiglutide is administered, any dose of albiglutide administered after that will be considered an overdose.

No data are available with regard to albiglutide overdose in humans. The highest recommended dose of albiglutide is 50 mg once weekly. During clinical studies of subjects with T2DM, the highest dose of albiglutide administered was 100 mg subcutaneously every 4 weeks for 12 weeks. This dose was associated with an increased frequency of nausea, vomiting, and headache. There is no specific antidote for overdose with albiglutide. In the event of a suspected overdose, the appropriate supportive clinical care should be instituted, as dictated by the subject's clinical status. Anticipated symptoms of an overdose may be severe nausea, vomiting, or headache. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the half-life of albiglutide (5 days).

6.8.2. Exenatide (Byetta)

Overdosage of exenatide is described in the latest Byetta product insert [**BYETTA** for injection, AstraZeneca 2015] as follows:

"In a clinical study of Byetta, three patients with type 2 diabetes each experienced a single overdose of 100 mcg 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. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms."

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because only healthy volunteers are eligible for study participation.

6.10. Lifestyle and/or Dietary Restrictions

6.10.1. Meals and Dietary Restrictions

Subjects must refrain from eating and drinking anything but water starting at approximately 10 pm the night before or with in 8 hours of the start of their MRI appointment until completion of all study assessments on imaging day. Subjects can drink water, but no more than 8 oz at a time and not within 2 hours of the appointment.

The subjects will be offered a small meal prior to leaving the site after each post-dose scanning session visit.

6.10.2. Caffeine, Alcohol, and Tobacco

- Subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) after 10 pm the evening prior to each MRI session day until completion of all study assessments on imaging day during each session.
- Subjects will abstain from alcohol for 24 hours prior to each dosing and each MRI session day until completion of all study assessments on imaging day during each session.
- Use of tobacco products is not allowed from 3 months prior to screening until after the final follow-up visit.

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription (excluding oral contraception) or non-prescription drugs (including vitamins and dietary or herbal supplements) during the study, unless in the opinion of the Investigator and Medical Monitor, the medication will not interfere with the study.

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., metoclopromide), narcotic analgesics (e.g., morphine), anticholinergics (e.g.,domperidone), anti-acids (e.g., pump inhibitors, H2 blockers), laxatives and drugs affecting pancreatic or hepatobiliary systems, or
- may stimulate or inhibit CNS (e.g., modafinil, dexamphetamine, methylphenidate, bromopheniramine, chlorpheniramine, clemastine, diphenhydramine, hyrdoxyzine)

may be withdrawn from the study at the discretion of the Investigator based on the reason (i.e., AE), duration of exposure and relative to the timing of the scans 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

7.1.1. Part A and B WITH Off-therapy MRI in Session 1

Procedure	Screen-ing		Session 1												Wash out	Session 2								F/U
	Week -4 to -1		Day 1				Day 5±1[m]	Day 8±1[m]							6-9 weeks	Day 1	Day 4±1[m]							Week 13
			Pre-MRI	MRI	Post MRI			-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI				-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI		
					0.5 h	1 h							0.5 h	1 h								0.5 h	1 h	
Visit (all out-patient)	1	2	3				4	5								6	7							8
Informed Consent	X																							
Demographics	X																							
Medical history[a]	X																							
Prior/Concomitant medication[b]	X	X	X				X	X								X	X							X
Complete physical	X																							
Brief physical								X									X							X
Vital signs	X	X	X		X		X	X					X	X		X	X					X	X	X
Urine Drug, Breath Alcohol/Cotinine	X	X	X				X	X								X	X							
12-lead ECG[e]	X																							
Pregnancy test (WCBP)[c]	X		X													X								X
HIV, Hep B and Hep C screen[d]	X																							
Clinical laboratory tests[e]	X															X								
TSH, free T4, triglycerides, amylase and lipase	X																							
Edinburgh Handedness Inventory	X																							
MSSQ-short	X																							
Mock fMRI[f]		X																						

Procedure	Screen-ing		Session 1													Wash out	Session 2									F/U
			Day 1				Day 5±1[m]	Day 8±1[m]									Day 1	Day 4±1[m]								
	Week -4 to -1		Pre-MRI	MRI	Post MRI			-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI			6-9 weeks		-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI		Week 13
					0.5 h	1 h							0.5 h	1 h									0.5 h	1 h		
Randomization		X																								
Dosing albiglutide or placebo[g]							X										X									
Dosing exenatide or placebo[g]										X										X						
MRI[h]				X								X										X				
Autonomic monitoring				X								X										X				
Electrogastrogram				X								X										X				
VAS			X		X						X		X								X		X			
MSAQ[i]					X								X										X			
Capillary blood glucose													X										X			
Fasting Plasma Glucose													X										X			
Snack[j]					X								X										X			
AE assessment[k]			<==========				<==========										<==========								X	
Discharge[l]						X									X										X	

a. Medical history includes alcohol/tobacco/caffeine usage.
b. Prior-Medications are defined as prescription or over-the counter medications taken within 30 days of Screening. Record concomitant medications and or changes.
c. WCBP is women of child-bearing potential. Serum pregnancy test at Screening. Urine pregnancy at other specified time points.
d. If test otherwise performed within 1 month prior to first dose of study treatment, testing at screening is not required.
e. See Table 2 for list of laboratory parameters. Unscheduled Safety Labs and ECGs can be done at any time if the Investigator considers the assessments appropriate for subject safety. .
f. Mock fMRI is performed on a separate day during the screening period. Scheduling should allow at least 1 week between the Mock fMRI and the next MRI scan.
g. Albiglutide, exenatide or placebo is administered according to randomization sequence.
h. All MRI include resting-state fMRI, ASL and MRS. Off-therapy MRI scan includes visual nauseogenic task fMRI and can be initiated once -assessments are completed. The on-therapy scan should be initiated 1 hr ±15min post the exenatide or exenatide placebo dose. Pre-scan procedure timings are suggested times to allow completion of activities. Post MRI procedure should be completed at the noted times ±15 min.

i. MSAQ is given following the VAS.
j. Subjects will be offered a snack prior to leaving the site.
k. Only events related to the Study Procedures meeting the SAE criteria are reported after screening and before dose on Session 1 Day 5.
l. Subjects should remain at the site for at least 1 hr after completion of MRI. All procedures and assessments must be complete prior to discharge. The Investigator will approve the release of the subject from the clinic, or will provide treatment for the standard of care as required.
m. The Post-dose MRI **MUST** be scheduled 4±1 days after the albiglutide or albiglutide placebo dose. The day of dosing albiglutide is counted as the first day.

7.1.2. Part A and B WITHOUT Off-therapy MRI in Session 1

	Screen-ing		Session 1								Wash out	Session 2												F/U
Procedure	Week -4 to -1		Day 1	Day 4±1[m]							6-9 weeks	Day 1				Day 5±1[m]	Day 8±1[m]							Week 13
				-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI 0.5 h	Post MRI 1 h		Pre-MRI	MRI	Post MRI 0.5 h	Post MRI 1 h		-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI 0.5 h	Post MRI 1 h	
Visit (all out-patient)	1	2	3	4								5				6	7							8
Informed Consent	X																							
Demographics	X																							
Medical history[a]	X																							
Prior/Concomitant medication[b]	X	X	X	X								X				X	X							X
Complete physical	X																							
Brief physical				X								X												X
Vital signs	X	X	X	X					X	X		X		X		X	X					X	X	X
Urine Drug, Breath Alcohol/Cotinine	X	X	X	X								X				X	X							
12-lead ECG[e]	X																							
Serum or urine pregnancy test (WCBP[c])	X		X									X												X
HIV, Hep B and Hep C screen[d]	X																							
Clinical laboratory tests[e]	X															X								
TSH, triglycerides, amylase and lipase	X																							
Edinburgh Handedness Inventory	X																							
MSSQ-short	X																							
Mock fMRI[f]		X																						
Randomization		X																						

	Screen-ing		Session 1									Wash out	Session 2													F/U
Procedure	Week -4 to -1		Day 1	Day 4±1[m]								6-9 weeks	Day 1				Day 5±1[m]	Day 8±1[m]								Week 13
				-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI				Pre-MRI	MRI	Post MRI			-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI			
									0.5 h	1 h					0.5 h	1 h							0.5 h	1 h		
Visit (all out-patient)	1	2	3	4									5				6	7								8
Dosing albiglutide or placebo[g]			X														X									
Dosing exenatide or placebo[g]						X														X						
MRI[h]								X						X								X				
Autonomic monitoring								X						X								X				
Electrogastogram								X						X								X				
VAS							X		X				X		X						X		X			
MSAQ[i]									X						X								X			
Capillary blood glucose									X														X			
Fasting Plasma Glucose									X														X			
Snack[j]									X						X								X			
AE assessment[k]			X	<==========									<==========				X	<==========							X	
Discharge[l]										X						X								X		

a. Medical history includes alcohol/tobacco/caffeine usage.
b. Prior-Medications are defined as prescription or over-the counter medications taken within 30 days of Screening. Record concomitant medications and or changes
c. WCBP is women of child-bearing potential. Serum pregnancy test at Screening. Urine pregnancy at other specified time points
d. If test otherwise performed within 1 month prior to first dose of study treatment, testing at screening is not required
e. See Table 2 for list of laboratory parameters. Unscheduled Safety Labs and ECGs can be done at any time if the Investigator considers the assessments appropriate for subject safety. The blood sample Session 2 Day 5 must be collected prior to dosing.
f. Mock fMRI session is performed on a separate day during the screening period. Scheduling should allow at least 1 week between the Mock fMRI and the next MRI scan.
g. Albiglutide, exenatide or placebo is administered according to randomization sequence.

h. All MRI include resting-state fMRI, ASL and MRS. Off-therapy MRI scan includes visual nauseogenic task fMRI and can be initiated once -assessments are completed. The on-therapy scan should be initiated 1 hr ±15min post the exenatide or exenatide placebo dose. Pre-scan procedure timings are suggested times to allow completion of activities. Post MRI procedure should be completed at the noted times ±15 min.
i. MSAQ is given following the VAS.
j. Subjects will be offered a snack prior to leaving the site.
k. Only events related to the Study Procedures meeting the SAE criteria are to be reported after screening and before dose on Session 1 Day 1.
l. Subjects should remain at the site for at least 1 hr after completion of MRI. All procedures and assessments must be complete prior to discharge. The Investigator will approve the release of the subject from the clinic, or will provide treatment for the standard of care as required.
m. The Post-dose MRI **MUST** be scheduled 4±1 days after the albiglutide or albiglutide placebo dose. The day of dosing albiglutide is counted as the first day.

7.2. Screening and Critical Baseline Assessments

The following demographic parameters will be captured: year of birth, gender, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

7.2.1. Motion Sickness Susceptibility Questionnaire Short (MSSQ-Short)

The MSSQ-Short will be completed by each potential subject at the screening visit. The questionnaire collects brief background information and consists of two sections [Appendix 6]. Section A collects the subject's childhood experience (before age 12) with travel and motion sickness. Section B collects the subjects experience of travel and motion sickness over the last 10 years [Golding, 2006].

7.2.2. Edinburgh Handedness Inventory

The Edinburgh Handedness Inventory consists of 10 items summarized as follows: (1) writing, (2) drawing, (3) throwing, (4) scissors, (5) toothbrush, (6) knife, without fork, (7) spoon, (8) broom (upper hand), (9) striking a match (match), and (10) opening box (lid). Respondents are required to indicate their hand preference and strength of preference [Appendix 5].

7.2.3. Mock fMRI

Subjects will be oriented to the visual motion sickness stimulus, while inside of a mock fMRI scanner (a plywood constructed replica). The subject will practice rating nausea severity and get comfortable with the scale, as well as their own limits with respect to severe nausea on the verge of vomiting. This will improve safety when they are then experiencing similar sensations inside the fMRI magnet.

The visual motion stimulation will be projected onto a screen with a field-of-view approximately 150°. This large unimpeded field of view is critical for inducing motion sickness with visual stimuli. A concave screen will be positioned 10 cm in front of their eyes, onto which visual stimuli will be projected, from behind. The nauseogenic stimulus will be a standardized visual presentation of alternating black (1.2 cm, 6.9° viewing angle) and white (1.85 cm, 10.6° viewing angle) stripes with left-to-right motion at ~62.5°/s. This left-to-right horizontal translation induces a vection sensation wherein subjects experience a false sensation of translating to the left. Such images simulate the visual input provided by a rotating optokinetic drum, commonly used to induce vection (illusory self- motion) and nausea. Symptoms severity will be rated as described below. Following the procedure, study personnel will debrief the subjects to ensure that they understand the rating levels and procedure.

0= no nausea, 1= minimal nausea, 2= mild nausea, 3= moderate nausea, 4= severe nausea

7.3. Endpoints

7.3.1. Magnetic Resonance Imaging

All MRI assessments will be acquired on a Siemens 3T system located at the Martinos Center for Biomedical Imaging. All Martinos scanners undergo quality assurance (QA) assessments every morning to ensure that fMRI signal drifts and variances are within limits and that signal spiking is not occurring.

Imaging scans will be reviewed by trained technologists and abnormal findings will be consulted with a radiologist. Subjects will be advised to seek consultation based on the radiologist's opinion.

Structural MRI:

Structural MRI data will be collected prior to all fMRI and MRS data collection using a T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) pulse sequence. These data will be used to help align functional data to the MNI space, while exploratory analysis of gray matter volume and cortical thickness can be related to functional brain response and symptom severity.

Functional MRI

All fMRI analyses will use a combination of tools, previously validated, and used in the Napadow Lab for the analysis of similar data. Tool packages will include: FSL (FMRIB Software Library; http://www.fsl.fmrib.ox.ac.uk/fsl/), AFNI (Analysis of Functional NeuroImages; http://afni.nimh.nih.gov/afni), and FreeSurfer (http://surfer.nmr.mgh.harvard.edu/).

<u>BOLD fMRI Resting</u>

Resting functional connectivity will be assessed using data acquired in the first 6 minutes of the vection task scan run , i.e. when the subject is resting, before any motion sickness provocation during the Off-therapy scan. For on-drug MRI visits, a separate 6-minute BOLD fMRI resting state scan will be performed, and subjects will verbally rate (0-100 NRS) their nausea intensity before and after this scan. Data will be analysed using validated independent component analysis (ICA) methods and seed voxel connectivity methods using functional localizer seeds obtained from the results of the motion sickness fMRI analyses.

<u>BOLD fMRI Visual Nauseogenic Task</u>

The 3T MRI will include a specially configured, open-design multichannel head coil. For the visual nauseogenic task BOLD fMRI scan run, subjects will lay supine inside the MRI scanner while visual stimuli are projected onto a screen encompassing their entire field of view. Subjects will be instructed to remain as still as possible, focus directly on the stimulus, and maintain as constant a rate of breathing as possible (i.e. not perform any respiratory maneuvers to decrease nausea). Subjects will be instructed to keep their eyes open and just let the nausea sensation evolve. The fMRI scan run will consist of a visual

fixation baseline for 6 min, followed by a visual presentation of alternating black/white stripes translating to the subjects' right field of view (gray background). Nausea produced by the visual vection signal will be rated using a button box. Once subjects rate a nausea level 4 (severe nausea) or 20 mins has passed, the stripes stimulation will be terminated and subjects will cross-hair fixate again for 6 min.

Arterial spin labeling (ASL)

ASL will be used to assess resting regional Cerebral Blood Flow (rCBF). The pseudo-Continuous ASL (pCASL) method will be used, which allows for adequate signal with whole brain coverage. rCBF maps will be contrasted, comparing flow maps under different drug conditions, and in comparison with a non-drug resting state (data collected during the off-therapy MRI visit, before the vection nausea task). Serial tagged and un-tagged image volumes will be subtracted, and the difference metric will be used in conjunction with an assumed T1 of gray matter tissue, partition coefficient, efficiency, and established equations for estimating rCBF.

Magnetic Resonance Spectroscopy (MRS) (GABA and glutamate)

GABA and glutamate magnetic resonance spectroscopy will be measured at rest. It will be measured prior to the motion sickness fMRI task run during the off-therapy scan. A newly developed motion-corrected 3D MRS sequence that reliably edits GABA and glutamate will be used for non-invasive brain mapping of neurotransmitter concentration. The field of view will cover key nausea processing areas such as insula, cingulate, and basal ganglia. The study will use a newly developed motion-corrected 3D magnetic resonance spectroscopy imaging (MRSI) sequence that, reliably evaluates glutamate/glutamine (GLX) concentration (FOV = 200x200x200, matrix=10x10x10, voxel 8 cc). Spectra will be fitted with LCModel and metabolic maps will be obtained from the fitted signals. The neurochemical maps will be transformed from anatomical subject space to MNI 152 standard space using non-linear registration (FNIRT, FSL). A novel group level analysis of spectroscopic data will be performed using a mixed effects model in the MNI152 standard space to detect significant regional changes of neurotransmitter levels under different drug and non-drug conditions.

7.3.2. Autonomic Monitoring

All peripheral autonomic physiological signals will be collected at 400 Hz using Chart Data Acquisition Software (ADInstruments) on a laptop equipped with a 16-channel Powerlab DAQ System (ADInstruments). Skin conductance level will be measured with MRI-compatible bipolar Ag/AgCl finger electrodes (MLT117F, ADInstruments) placed on the palmar aspect of the second and fourth fingers of the nondominant (left) hand, prior to the MRI session. Subjects' ECG signal will be collected with an MRI-compatible Patient Monitoring system (Biopac 150, Biopac Systems Inc.) through MRI-compatible electrodes (VerMed, Bellows Falls) placed on the chest.

7.3.3. Nausea severity psychophysics

Nausea ratings will be collected during motion sickness provocation using a 0-4 numerical rating scale (NRS). One member of the team will instruct the subject on how

to use the button box to rate his/her nausea sensation. For the mock scanner training, once every 15 seconds, a sensory cue will be applied, reminding the subject to rate their nausea severity. During the actual fMRI experiment, subjects will rate nausea severity using the button box, as they experience it, and ratings increase events will be used to guide data analysis. We will ask the subject to press buttons on a MRI compatible button-box to rate nausea using the following scale:

- Press the thumb button if you do not feel any nausea;
- Button 1 (index finger) if **minimal** nausea is experienced;
- Button 2 (middle finger) if **mild** nausea is experienced;
- Button 3 (ring finger) if **moderate** nausea is experienced;
- Button 4 (pinky finger) if **severe** nausea is experienced;

The subject will be instructed that, when button 4 is pressed, signifying that severe nausea is experienced, the nauseating stimulus (moving lines) will be stopped. If, due to any reason, the subject wants to stop the experiment before, he/she can squeeze the squeeze bulb, the experiment will stop and the subject will be taken out of the mock or real fMRI magnet.

7.3.4. Subject assessment of nausea

Motion Sickness Assessment Questionnaire (MSAQ)

Following the visual nauseogenic task, subjects will complete the Motion Sickness Assessment Questionnaire (MSAQ) (Appendix 8), which quantifies the severity of different dimensions of nausea induced by motion sickness [Gianaros, 2001]

Visual Analogue Scale (VAS)

Each subject will complete a VAS to record their perception of stomach fullness, hunger, nausea, bloating and abdominal pain. The VAS (Appendix 7) will be represented by lines, 100mm in length, anchored with words describing the most negative rating on the left and the most positive rating on the right. The site will be provided with paper copies of the scale to administer at each MRI session. Subjects will complete a VAS form approximately 30 min before and approximately 30 min after each imaging scan session.

7.3.5. Electrogastrogram

Electrogastrography (EGG) is a technique for recording gastric myoelectrical activity using cutaneous electrodes (non-invasively) by placing three EKG-type electrodes in the epigastrium in standard positions. Signals will be obtained with appropriate amplification and filtering during the MRI scans. The EGG summates the ongoing gastric slow wave and plateau potential activity of the stomach. Collection of EGG during the MRI is experimental and may not progress if deemed uninterpretable.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests such as vital signs, physical exams

and laboratory safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

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

The definitions of an AE or SAE can be found in Appendix 3 (Section 12.3).

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

Nausea during the visual nauseogenic task is expected and will not be considered an AE, and will be reported as an endpoint. Any other untoward medical events occurring during the visual nauseogenic task should be reported as an AE/SAE if meets the definition as noted in Appendix 3 (Section 12.3).

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, 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 CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.
- 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 3.

7.4.1.2. Method of Detecting AEs and SAEs

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

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

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

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1 and Section 7.4.1.4), will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3 (Section 12.3).

7.4.1.4. Adverse Events (AE) of Special Interest

In the Phase IV clinical development program, AEs of special interest included several areas of safety related concern for the T2DM population, particularly for a GLP-1R agonist such as albiglutide. Specific eCRF pages will be used to capture additional details for the following AEs of special interest:

- Hypoglycemic events
- Liver events
- CV events
- Injection site reactions
- Potential systemic allergic reactions
- Pancreatitis
- Medullary thyroid cancer
- Pneumonia
- Atrial fibrillation/atrial flutter

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

- GI events
- Malignant neoplasms, including pancreatic cancers
- Appendicitis

7.4.1.5. 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

- Details of all pregnancies in female subjects will be collected after the start of dosing and until the follow-up visit.
- If a pregnancy is reported then the Investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

7.4.3. Hypoglycemia

Although not anticipated in the healthy volunteer population, hypoglycemia is a risk with treatment of a GLP-1 receptor agonist. Capillary blood glucose measures will be taken after each post dose MRI. A capillary blood glucose measure should be taken any time a subjects present with signs and or symptoms of hypoglycaemia and the subject treated with dietary therapy (i.e. a small meal), a carbohydrate load (e.g., glucose tables or orange juice), or any other required treatment at the discretion of the Investigator. Subjects will be asked to eat a snack after the investigational drug administration sessions.

7.4.4. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems and skin. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum assessments of the skin (including injection site), lungs, cardiovascular system, and abdomen (liver and spleen).
- Height weight 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.

7.4.5. Discharge

Subjects will remain at the clinic for at least 1.0 hours after the dose of medication or completion of scan whichever is later. All procedures and assessments must be complete before the subject is released. The Investigator or medically qualified site staff will approve the release of the subject from the clinic or will provide treatment as per standard of care as required.

7.4.6. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure and pulse rate.

- For all vital signs, single measurement will be performed at time points specified in Time and Events Tables (Section 7.1).
- Vital sign measurements can be repeated once if clinically significant changes or machine error occur. Out of range blood pressure and heart rates will be repeated at the Investigator's discretion.

7.4.7. Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at screening using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.4.8. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 1, 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 labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. 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 CRF.

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, entered into the eCRF and sent to GSK via lab data transfer.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 2

Table 2 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*
	RBC Count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Hematocrit		Monocytes
			Eosinophils
			Basophils

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine
• eGRF (MDRD)</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
</table>
</td></tr>
<tr><td>Glycemic parameters</td><td>Capillary blood glucose (for patient safety only)
Fasting plasma glucose</td></tr>
<tr><td>Routine Urinalysis</td><td>• Specific gravity
• pH, glucose, protein, blood and ketones by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening Tests</td><td>• TSH, free T4, triglycerides, amylase and lipase
• HIV, Hepatitis B and C Screen
• Alcohol/Cotinine and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
• Serum or urine hCG Pregnancy test (as needed for women of child bearing potential) [2]
• FSH and estradiol-for women< 60 yrs and <12 months postmenarchal and do not agree to effective method of birth control</td></tr>
<tr><td colspan="2">NOTES :
1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.1 and Appendix 2.
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.</td></tr>
</table>

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.

7.5. 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.

8. DATA MANAGEMENT

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

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

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

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

The study has 2 parts – Part A and Part B. After Part A, a review of safety data as well as fidelity of imaging and physiological (e.g. EGG) measures taken during the different MRI scan sessions will be performed. Part A data review is part of the exploratory nature of this study and could result in refinement of endpoints and statistical analysis. A decision to enroll 4 additional subjects, and/or adjust Part B design (e.g., change in MRS pulse sequence), will be made based on imaging evaluators' judgment in consultation with the PI and Sponsor.

9.1. Hypotheses

No primary hypothesis will be pre-specified due to the exploratory nature of the study.

9.2. Sample Size Considerations

A total from Parts A and B of 24 or 28 randomized subjects with valid MRI data that could be pooled for analysis will be targeted for the entire study. Part A will initially randomize 4 subjects. Based on data review from the initial 4 subjects, additional 4 subjects may be randomized for Part A. The decision to enroll another Cohort of 4 subjects in Part A will be based on imaging evaluators' judgment in consultation with the PI and Sponsor.

Part B will randomize 20 subjects.

Subjects will be randomized according to treatment sequences described in Section 4.2.

9.2.1. Sample Size Assumptions & Size Sensitivity

Accurate prospective determination of experimental power and sample size is difficult for fMRI experiments because many idiosyncratic factors (e.g. scanner sequence, brain region under investigation, task paradigm) can have a large influence on the effective signal-to-noise. In addition, there is little similar published work available to act as a guide. A target sample size in the range 12 to 24 is recommended by Desmond and Glover [Desmond, 2002] for fMRI experiments; though it should be noted that advances in acquisition technology and analysis techniques in the last thirteen years have significantly increased signal-to-noise, meaning the upper bound of the estimate (N≈24) may now be somewhat inflated. Importantly, the sample size chosen for this study is consistent with the sample size previously published by the Martinos Center group in their nausea neuroimaging study [Napadow, 2013].

9.2.2. Sample Size Re-estimation or Adjustment

If subjects prematurely discontinue the study or individual subject technical issues arise, subjects will be replaced at the discretion of the imaging evaluators' judgment in consultation with the Investigator and Sponsor. Subjects will be assigned to the same treatment sequence in order to meet the target number of subjects. Within each phase or part, the randomization of subjects should first be completed before subjects are replaced. Data from subjects who are replaced will be used only for safety analysis.

Issues that may lead to exclusion of data from analysis could include excessive head-motion by the subject during a scan, identifiable artifacts on the brain images arising from problems with the scanner, and issues with the simultaneous physiological recordings (poor signals due to interference, or sensors moving out of position during a scan). Data quality will be iteratively assessed by technical imaging site staff throughout the study in a blinded manner. If some subjects' data is sub-standard and therefore needs to be excluded, additional recruiting and testing may be conducted. Data quality findings will be documented.

9.3. Data Analysis Considerations

There will be 4 fMRI and 3 MRS data points as shown in the table below:

Treatment Period [a]			Albiglutide	Exenatide
Day Relative to Period Start [b]	1 Off-therapy	1 Off-therapy	8 At T-max	8 At T-max
Visual Nauseogenic Task	No	Yes	No	No
MRI Data Point (DP)	DP1	DP2	DP3	DP4

Treatment Period [a]			Albiglutide	Exenatide
Resting State BOLD fMRI	✓		✓	✓
Nauseogenic task based BOLD fMRI		✓		
ASL	✓		✓	✓
MRS	✓		✓	✓

[a] The order of the treatment periods will be randomized.
[b] The day is relative to start of the Treatment Period.

For each subject, the Off-therapy Day 1 assessment(s) (DP1 and/or DP2 in table above) during the dosing/imaging sessions will serve as the baseline fMRI assessment.

Nauseogenic task BOLD signal (DP2,), will be assessed only during the off-therapy fMRI session. For the BOLD endpoint, the main contrasts of interest are the differences in the connectivity between albiglutide and off-therapy (DP3-DP2), between Exenatide and off-therapy (DP4-DP2), and between Albiglutide and Exenatide (DP3-DP4).

For resting state analysis rCBF ASL endpoints, the contrasts of interest are the differences DP3-DP1, DP4-DP1, and DP4-DP3. Similarly, for GABA and Glutamate concentrations, the main contrasts of interest are the differences DP3-DP1, DP4-DP1, and DP4-DP3.

The vection-induced nausea will provide a reference to regions of nausea associated brain activity. A group map will be calculated as in the previous Martinos Center study, and regions of interest (ROI) will be defined from the group map. These ROIs will then be used to perform masked comparison analyses for rCBF and MRS (where possible) data between the albiglutide vs exanatide and drug vs no-drug conditions. Such targeted analyses will allow for greater power than whole brain analyses which will need to be more stringently corrected for multiple comparisons.

There will be no imputation for missing data. Subjects who only partially complete the study may be included in some of the analyses where appropriate, depending on which data are available and which are missing.

Summary statistics (including number of subjects, mean, median, min, max, SD, SE) will be reported for continuous variables. The frequency and percentage will be used to summarize categorical variables.

Functional MRI Data

Pre-processing steps will include motion correction carried out by sequentially aligning each time-point across the series with a single target scan, using a rigid-body registration algorithm. Further pre-processing steps may also include slice timing corrections and

spatial smoothing. To ensure each subject's parameter estimate maps (e.g. following general linear modeling, see below) lie in a common anatomical space, an initial affine registration will be applied from the native low-resolution Echo Planar Imaging (EPI) data to the respective high resolution T1-weighted scan or a mean image of EPI scans. These spatially normalized subject-specific statistics will then undergo a further alignment onto a common atlas space such as the Montreal Neurological Institute (MNI) coordinate system.

Following pre-processing, several sets of statistical analyses will then be conducted, with standard methods (e.g. application of the General Linear Model, Independent Components Analysis) with the addition of sophisticated noise-modeling methods, derived from the acquired physiological data (respiratory/cardiac). Data will be examined at both a whole-brain and regions of interest (ROI) level, with ROIs defined by intersecting anatomical label masks (based on standard atlases such as the well known Harvard-Oxford Atlas) with clusters derived from the group data. Other exploratory methods, such as Multi-Voxel Pattern Analysis (MVPA) may also be employed, as appropriate. Analyses will take advantage of individual subject nausea rating responses during stimulation, for both stimulus-based (distinct windows), and percept based (increasing nausea transitions) analyses, as in previous publications [Napadow, 2013]. Results from the off-therapy motion sickness task fMRI scan will be used to define ROI's of nausea-related brain circuitry in the same individuals who will also experience on-therapy nausea MRI scanning. These ROI's will be used to guide analysis of the fMRI, ASL, and MRS data from both on-therapy and off-therapy scan sessions. Group analyses will include both the entire on-drug group and, in a separate analysis, the subgroup of subjects who were on-drug and perceived nausea during the scan. This will allow for an investigation of sub-threshold changes in brain physiology due to the drug as well as more specific analyses targeting nausea perception as a result of drug intake.

Arterial spin labeling (ASL) data will be pre-processed similarly for motion correction, and tagged and un-tagged images will be subtracted and used to calculate regional cerebral blood flow (rCBF) using validated equations for pulsed continuous ASL (pCASL). ASL data acquired while the subject was experiencing nausea will then be contrasted with nausea-free scans acquired at the beginning of the Off-therapy MRI session (i.e. before the vection nausea task), to evaluate brain rCBF response during drug-induced nausea perception.

9.3.1. Analysis Populations

For this exploratory study, the analysis set will include subjects who have valid data.

9.3.2. Part A Data Review

There are 2 potential interim data reviews during the study. The first interim data review will be performed after all MRI assessments from 4 subjects have been collected and cleaned. Based on results from interim review, a decision to randomize 4 more subjects for Part A, and/or adjust Part B design (e.g., change in MRS pulse sequence), will be made based on imaging evaluators' judgment in consultation with the PI and Sponsor.

A second interim data review will occur only if a decision to randomize 4 more for Part A is made after initial review of results from the first 4 subjects. This second review, should it occur, will use all data from 8 subjects. Once the required number of subjects has been randomized for an upcoming data review, randomization of additional subjects will be put on hold. Randomization will resume after a decision to continue the study is made.

9.4. Key Elements of Analysis Plan

Data from Parts A and B, as appropriate, will be pooled for final analysis. For comparisons between Albiglutide and exenatide, analysis of variance (ANOVA) will be used to analyze quantifiable endpoints with treatment and period as fixed effects, and subject as random effect. The contrast of interest for BOLD, ASL and MRS endpoints described in Section 9.3 will be tested using this model.

Pearson's and Spearman's correlation coefficients will be used to review relationships between selected quantifiable end points.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

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

10.3. Quality Control (Study Monitoring)

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

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

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

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the Investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the Investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the Investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all Investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the Investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the Investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The Investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the Investigator is no longer associated with the site.

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

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

GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate.

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

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

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.8. Review Committees

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

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12. APPENDICES

12.1. Appendix 1 : Abbreviations and Trademarks

Abbreviations

AE	Adverse event
AFNI	Analysis of Functional NeuroImages
ALT	Alanine aminotransferase
ASL	Arterial spin labeling
BMI	Body mass index
BOLD	Blood oxygen level dependent
CI	Confidence interval
Cmax	Maximum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CV	Cardiovascular
DF	Dominant frequency
DP	Dominant power
DPP-IV	Dipeptidyl peptidase-IV
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EGG	Electrogastrography
EMA	European Medicines Agency
EPI	Echo Planar Imaging
EU	European Union
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
FRP	Females of reproductive potential
FSH	Follicle stimulating hormone
FSL	FMRIB Software Library
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GI	Gstrointestinal
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
GMA	Gastric myoelectrical activity
GSK	GlaxoSmithKline
h	Hour
hCG	Human chorionic gonadotrophin
HIV	Human immunodeficiency virus
HV	Healthy volunteers
IB	Investigator brochure
ICA	Independent component analysis
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IRB	Institutional Review Board
IVRS	Interactive voice response system
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
MNI	Montreal Neurological Institute
MP-RAGE	Magnetization-prepared rapid gradient-echo
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MRSI	Magnetic resonance spectroscopy imaging
MSAQ	Motion Sickness Assessment Questionnaire
MSDS	Material Safety Data Sheet
MSSQ	Motion Sickness Susceptibility Questionnaire
MTC	Medullary thyroid carcinoma
MVPA	Multi-Voxel Pattern Analysis
NRS	Numerical rating scale
PCASL	Pseudo-Continuous ASL
PD	Pharmacodynamic
PI	Prescribing information
PK	Pharmacokinetic
PPAR	Peroxisome proliferator-activated receptor
QA	Quality assurance
rCBF	Regional cerebral blood flow
ROI	Regions of interest
SAE	Serious adverse event
SC	Subcutaneous
SD	Single dose
SOP	Standard operating procedure
SRM	Study reference manual
SU	Sulfonylurea
T&E	Time and Events
T1/2	Terminal phase half-life
T2DM	type 2 diabetes mellitus
Tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
VAS	Visual analogue scale

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
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SAS
WinNonlin

12.2. Appendix 2 : Liver Safety Required Actions and Follow up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure subject safety and to 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 I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• 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, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td>• Viral hepatitis serology[3]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of 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
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • 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	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 CRF forms.

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

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12.3. Appendix 3 : Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

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

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

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the

Investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

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

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

a. Results in death

b. Is life-threatening

NOTE:

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

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

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

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

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

- Myocardial infarction/unstable angina
- Congestive heart failure

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

12.3.4. 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 CRF
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.3.5. 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 CRF. • The Investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.6. 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.

SAE reporting to GSK via paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail • Initial notification via the telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via PIMS

• Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the Medical Monitor:
  • SAE listing
  • Demographic listing
  • Study treatment listing
• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
• If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the Medical Monitor. The site will enter the SAE data into PIMS as soon as the system becomes available.

12.4. Appendix 4: Collection of Pregnancy Information

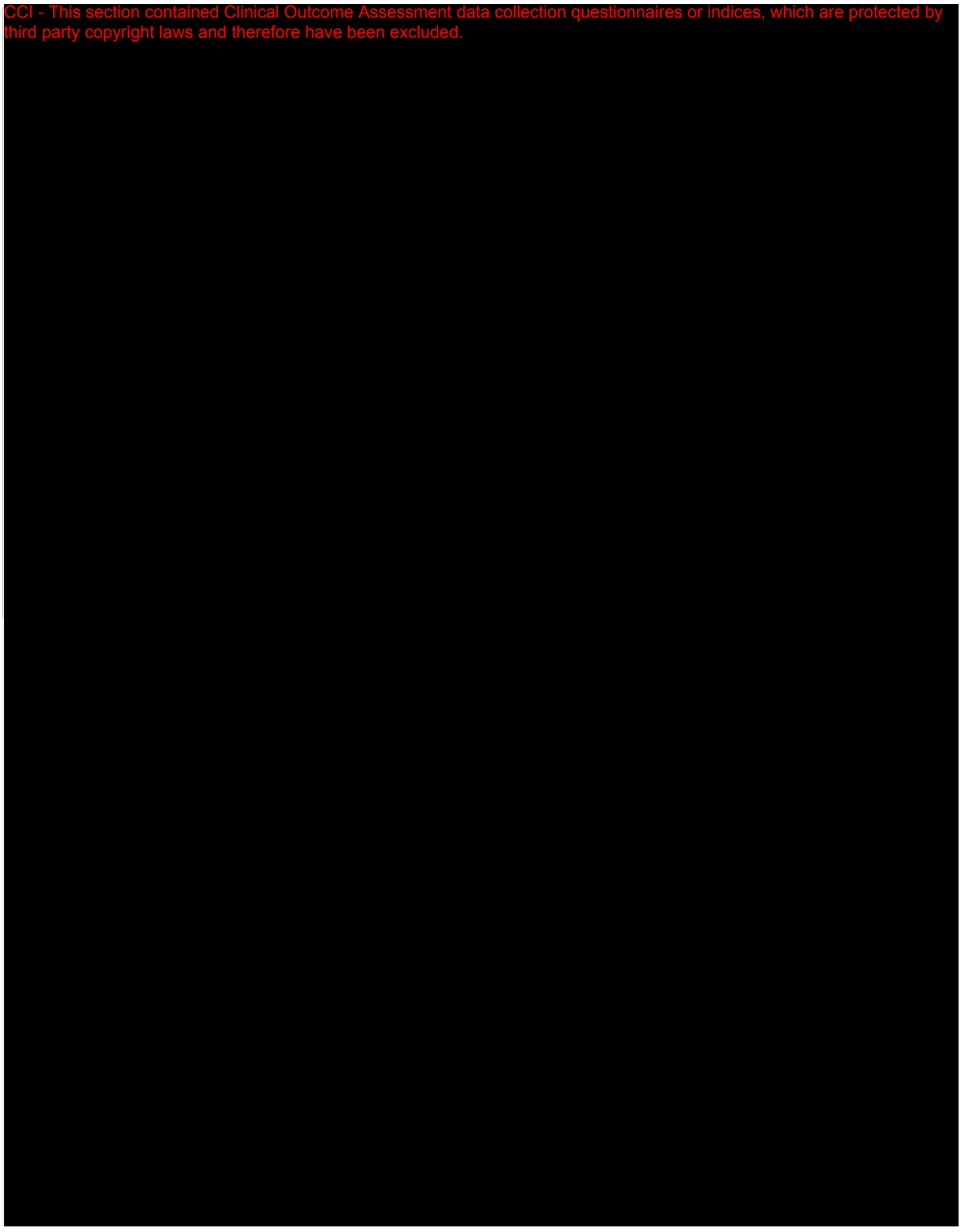
For female subjects of reproductive potential:

- Any female subjects who become pregnant while participating will be withdrawn from the study.
- The 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 3. 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.

12.5. Appendix 5 : Edinburgh Handedness Inventory

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.

12.6. Appendix 6 : Motion Sickness Susceptibility Questionnaire



12.7. Appendix 7 : Visual Analog Scale

Mark each symptom line with a vertical line where you believe each of the following words best describes how you currently feel (PLEASE make ONLY ONE VERTICAL LINE for each symptom).

a. STOMACH FULLNESS

___ mm

NOT FULL AT ALL — COMPLETELY FULL

b. HUNGER

___ mm

NONE — EXTREME

c. NAUSEA

___ mm

NONE — SEVERE

d. BLOATING

___ mm

NONE — SEVERE

e. ABDOMINAL PAIN

___ mm

NONE — SEVERE

12.8. Appendix 8 : Motion Sickness Assessment Questionnaire (MSAQ)

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.

12.9. Appendix 9 : Country Specific Requirements

No country-specific requirements exist.

12.10. Appendix 10 : Protocol Changes

Protocol Amendment Number 1

Protocol Amendment Number 1 is applicable to all clinical study centers participating in this study. This is a single center study. Protocol changes specified in Amendment Number 1 are summarized as follows:

- Inclusion criterion #4 was updated to reflect the nausea susceptibility score of >17 when using the MSSQ short form as described in the protocol. The prior criterion erroneously reflected the nausea susceptibility score when using the MSSQ long form.

- Exclusion criterion #4 was expanded to allow the use of MRI safe glasses for subjects requiring vision correction.

- A statement was added to allow rescreening with approval from Medical Monitor

- Exploratory endpoint for GMA was updated to reflect output of EGG instrument. Flexibility was added to remove EGG as an endpoint if not able to collect during MRI

- The Time and Events Table was updated:

    - The Screening Period was updated to allow more flexibility in the scheduling of the screening procedures.

    - Clarification of the timings of the Mock MRI and windows for the pre and post MRI procedures was added.

    - The statement that safety labs must be done in the fasting state was removed as measurements requiring fasting are described in Section 7.4.8 Clinical Laboratory Assessments

    - Safety labs for Session 2 (Part A and B <u>WITHOUT Off-therapy MRI</u> in Session 1) were changed to be collected on Day 5 prior to dosing

    - Missing rows to indicate EGG in Table 7.1.2 and Randomization in both tables were added

- The time period to stop food and drink except water was updated to align with IRB requirements

- Administrative changes including updating the medical monitor roles and email addressed as well as minor typographical errors were corrected.

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

Medical Monitor/Sponsor Information Page:

Role	Name	Day Time Phone Number and email address
Primary Medical Monitor	PPD	PPD
Secondary Medical Monitor		
SAE contact information		

PROTOCOL SYNOPSIS

Objectives/Endpoints

Objectives	Endpoints
Primary	
• To explore the effect of single dose 50 mg albiglutide compared to single dose 10 μg exenatide on regional brain activity and connectivity associated with nausea in healthy volunteers	• Resting-state BOLD signal (fMRI) • Regional cerebral blood flow (rCBF) (fMRI-ASL) • Glutamate concentration in nausea-associated brain regions (MRS) • GABA concentration in nausea-associated brain regions (MRS)
Secondary	
• To evaluate autonomic effects of single dose 50 mg albiglutide compared to single dose 10 μg exenatide • To assess safety and tolerability of single dose 50 mg albiglutide and single dose 10 μg exenatide	• Heart rate, heart rate variability, respiratory rate, ECG intervals, blood pressure, skin conductance level • Vital signs, clinical laboratory tests, adverse events, Nausea ratings scale, GI-VAS and MSAQ
Exploratory	
• To evaluate gastric myoelectrical activity (GMA) of single dose 50 mg albiglutide compared to single dose 10 μg exenatide	• GMA~~: Dominant power (DP), Dominant frequency (DF), % time spent in 3 frequency bands (Bradygastria, Normal, Tachygastria) and Ratio of power in post-task versus pre-task~~ • GMA: **description of frequency region** (Bradygastria, Normal, Tachygastria)

Study Design (diagram)

Screening	
~~Week -4 to -3~~	~~Week -2~~
Week -4 to -1	

Treatment arms and Duration

In either Part A or Part B, the total duration of a subject's participation is approximately 15 – 19 weeks, assuming ~~3~~ **up** to 4 weeks for screening, 8 days each for Session 1 and Session 2, 6 to 9 weeks for washout, and a 4 weeks post last treatment follow-up.

PROTOCOL

Section 3 Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	
• To explore the effect of single dose 50 mg albiglutide compared to single dose 10 μg exenatide on regional brain activity and connectivity associated with nausea in healthy volunteers	• Resting-state BOLD signal (fMRI) • Regional cerebral blood flow (rCBF) (fMRI-ASL) • Glutamate concentration in nausea-associated brain regions (MRS) • GABA concentration in nausea-associated brain regions (MRS)
Secondary	
• To evaluate autonomic effects of single dose 50 mg albiglutide compared to single dose 10 μg exenatide • To assess safety and tolerability of single dose 50 mg albiglutide and single dose 10 μg exenatide	• Heart rate, heart rate variability, respiratory rate, ECG intervals, blood pressure, skin conductance level • Vital signs, clinical laboratory tests, adverse events, Nausea ratings scale, GI VAS, and MSAQ
Exploratory	
• To evaluate gastric myoelectrical activity (GMA) of single dose 50 mg albiglutide compared to single dose10 μg exenatide	• ~~GMA: Dominant power (DP), Dominant frequency (DF), % time spent in 3 frequency bands (Bradygastria, Normal, Tachygastria) and Ratio of power in post-task versus pre-task~~ • GMA: **description of frequency region** (Bradygastria, Normal, Tachygastria)

Section 4.1 Overall Design

(Diagram)

Screening	
~~Week -4 to -3~~	~~Week -2~~
Week -4 to -1	

For all MRI sessions, subjects must fast overnight and will be instructed to refrain from eating and drinking ~~after 9 pm of the evening before each session~~ **anything but water**

starting at approximately 10 pm the night before or with in 8 hours of the start of their MRI appointment

Section 4.2 Treatment Arms and Duration

All doses will be given in the morning. For all MRI sessions subjects must fast overnight and will be required to refrain from eating and drinking **anything but water starting at approximately 10 pm the night before or with in 8 hours of the start of their MRI appointment** ~~after 9 pm of the evening prior to each MRI scan visit~~ (see Section 6.10.1).

Section 5.1 Inclusion Criteria

4. Motion Sickness Susceptibility Questionnaire (MSSQ-**short**) Screening score >~~60~~ **17** and mock fMRI nausea rating ≥2(See Appendix 6)

Section 5.2 Exclusion Criteria

4. ~~Use of eyeglasses during fMRI~~. Subjects requiring visual correction to participate in visual task that cannot be corrected with contact lenses **or MRI safe glasses**.

Section 5.3 Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events. **Subjects can be rescreened once if agreed after discussion with the Medical Monitor.**

Section 6.10.1 Meals and Dietary Restrictions

Subjects must refrain from eating and drinking **anything but water starting at approximately 10 pm the night before or with in 8 hours of the start of their MRI appointment** ~~after 9 pm of the evening prior to each MRI session day~~ until completion of all study assessments on imaging day. Subjects can drink water, but no more than 8 oz at a time and not within 2 hours of the appointment.

Section 6.10.2 Caffeine, Alcohol, and Tobacco

- Subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) after ~~9:00~~ **10** pm the evening prior to each MRI session day until completion of all study assessments on imaging day during each session.

Section 7.1 Time and Events Table

Section 7.1.1 Part A and B <u>WITH Off-therapy MRI</u> in Session 1

Procedure	Screen-ing		Session 1												Wash out	Session 2									F/U
			Day 1				Day 5±1[m]	Day 8±1[0]								Day 1	Day 4±1[0]								Week 13
	~~Week -4 to -3~~ **Week -4 to -1** ~~Week -1~~		Pre-MRI	MRI	Post MRI 0.5 h	Post MRI 1 h		-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI 0.5 h	Post MRI 1 h	6-9 weeks		-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI 0.5 h	Post MRI 1 h	
Visit (all out-patient)	1	2	3				4	5								6	7								8
Informed Consent	X																								
Demographics	X																								
Medical history[a]	X																								
Prior/Concomitant medication[b]	X	X	X				X	X								X	X								X
Complete physical	X																								
Brief physical								X									X								X
Vital signs	X	X	X		X		X	X					X	X		X	X					X	X		X
Urine Drug, Breath Alcohol/Cotinine	X	X	X				X	X								X	X								
12-lead ECG[0]	X																								
Pregnancy test (WCBP)[0]	X		X													X									X
HIV, Hep B and Hep C screen[0]	X																								
Clinical laboratory tests[0]	X															X									
TSH, free T4, triglycerides, amylase and lipase	X																								
Edinburgh Handedness Inventory	X																								
MSSQ-short	X																								
Mock fMRI[0]		X																							

Procedure	Screen-ing		Session 1													Wash out	Session 2									F/U
			Day 1				Day 5±1[m]	Day 8±1[0]								6-9 weeks	Day 1	Day 4±1[0]								Week 13
	~~Week -1~~ ~~Week -4 to -3~~ **Week -4 to -1**		Pre-MRI	MRI	Post MRI 0.5 h	Post MRI 1 h		-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI 0.5 h	Post MRI 1 h			-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI 0.5 h	Post MRI 1 h	
Randomization		**X**																								
Dosing albiglutide or placebo[0]							X										X									
Dosing exenatide or placebo[0]										X										X						
MRI[0]				X								X										X				
Autonomic monitoring				X								X										X				
Electrogastrogram				X								X										X				
VAS			X		X						X		X								X		X			
MSAQ[0]					X								X										X			
Capillary blood glucose													X										X			
Fasting Plasma Glucose													X										X			
Snack[0]					X								X										X			
AE assessment[0]			<==========>				<==========>										<==========>									X
Discharge[0]						X									X										X	

a. Medical history includes alcohol/tobacco/caffeine usage.
b. Prior-Medications are defined as prescription or over-the counter medications taken within 30 days of Screening. Record concomitant medications and or changes.
c. WCBP is women of child-bearing potential. Serum pregnancy test at Screening. Urine pregnancy at other specified time points.
d. If test otherwise performed within 1 month prior to first dose of study treatment, testing at screening is not required.
e. See Table 2 for list of laboratory parameters. Unscheduled Safety Labs and ECGs can be done at any time if the Investigator considers the assessments appropriate for subject safety. ~~Safety labs must be done in fasting state.~~
f. Mock fMRI is performed on a separate day **during the screening period. Scheduling should allow at least 1 week between the Mock fMRI and the next MRI scan.**
g. Albiglutide, exenatide or placebo is administered according to randomization sequence.
h. All MRI include resting-state fMRI, ASL and MRS. Off-therapy MRI scan includes visual nauseogenic task fMRI and can be initiated once -assessments are completed**. The on-therapy scan should be initiated 1 hr ±15min post the exenatide or exenatide placebo dose. Pre-scan procedure timings are suggested times to allow completion of activities. Post MRI procedure should be completed at the noted times ±15 min.**

Section 7.1.2 Part A and B <u>WITHOUT Off-therapy MRI</u> in Session 1

	Screen-ing		Session 1								Wash out	Session 2												F/U
Procedure	~~Week -4 to -1~~ **Week -4 to -3** ~~Week -1~~		Day 1	Day 4±1[m]							6-9 weeks	Day 1				Day 5±1[m]	Day 8±1[m]							Week 13
				-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI			Pre-MRI	MRI	Post MRI			-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI		
									0.5 h	1 h				0.5 h	1 h								0.5 h	1 h	
Visit (all out-patient)	1	2	3	4								5				6	7							8
Informed Consent	X																							
Demographics	X																							
Medical history[a]	X																							
Prior/Concomitant medication[b]	X	X	X	X								X				X	X							X
Complete physical	X																							
Brief physical				X								X												X
Vital signs	X	X	X	X					X	X		X		X		X	X					X	X	X
Urine Drug, Breath Alcohol/Cotinine	X	X	X	X								X				X	X							
12-lead ECG[e]	X																							
Serum or urine pregnancy test (WCBP[c])	X		X									X												X
HIV, Hep B and Hep C screen[d]	X																							
Clinical laboratory tests[e]	X											~~X~~				**X**								
TSH, triglycerides, amylase and lipase	X																							
Edinburgh Handedness Inventory	X																							
MSSQ-short	X																							
Mock fMRI[f]		X																						
Randomization		**X**																						

	Screen-ing		Session 1								Wash out	Session 2													F/U
Procedure	~~Week -4 to -3~~ ~~Week -1~~ **Week -4 to -1**		Day 1	Day 4±1[m]							6-9 weeks	Day 1				Day 5±1[m]	Day 8±1[m]								Week 13
				-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI			Pre-MRI	MRI	Post MRI			-2 h	-0.5 h	0 h	0.5 h	1 h	Post MRI		
									0.5 h	1 h				0.5 h	1 h								0.5 h	1 h	
Visit (all out-patient)	1	2	3	4								5				6	7								8
Dosing albiglutide or placebo[g]			X													X									
Dosing exenatide or placebo[g]						X													X						
MRI[h]								X					X								X				
Autonomic monitoring								X					X								X				
Electrogastogram								**X**					**X**								**X**				
VAS							X		X			X		X						X		X			
MSAQ[i]									X					X								X			
Capillary blood glucose									X													X			
Fasting Plasma Glucose									X													X			
Snack[j]									X					X								X			
AE assessment[k]			X	<==========								<==========				X	<==========								X
Discharge[l]										X					X									X	

a. Medical history includes alcohol/tobacco/caffeine usage.
b. Prior-Medications are defined as prescription or over-the counter medications taken within 30 days of Screening. Record concomitant medications and or changes
c. WCBP is women of child-bearing potential. Serum pregnancy test at Screening. Urine pregnancy at other specified time points
d. If test otherwise performed within 1 month prior to first dose of study treatment, testing at screening is not required
e. See Table 2 for list of laboratory parameters. Unscheduled Safety Labs and ECGs can be done at any time if the Investigator considers the assessments appropriate for subject safety. **The blood sample Session 2 Day 5 must be collected prior to dosing**. ~~Safety labs must be done in fasting state~~
f. Mock fMRI session ~~and MSSQ task are~~ **is** performed on a separate day. **Scheduling should allow at least 1 week between the Mock fMRI and the next MRI scan.**~~once all other entry criteria met.~~
g. Albiglutide, exenatide or placebo is administered according to randomization sequence.

h. All MRI include resting-state fMRI, ASL and MRS. Off-therapy MRI scan includes visual nauseogenic task fMRI and can be initiated once -assessments are completed. **The on-therapy scan should be initiated 1 hr ±15min post the exenatide or exenatide placebo dose. Pre-scan procedure timings are suggested times to allow completion of activities. Post MRI procedure should be completed at the noted times ±15 min.**
i. MSAQ is given following the VAS.
j. Subjects will be offered a snack prior to leaving the site.
k. Only events related to the Study Procedures meeting the SAE criteria are to be reported after screening and before dose on Session 1 Day 1.
l. Subjects should remain at the site for at least 1 hr after completion of MRI. All procedures and assessments must be complete prior to discharge. The Investigator will approve the release of the subject from the clinic, or will provide treatment for the standard of care as required.
m. The Post-dose MRI **MUST** be scheduled 4±1 days after the albiglutide or albiglutide placebo dose. The day of dosing albiglutide is counted as the first day.

Section 7.4.7 Electrogastrogram

Collection of EGG during the MRI is experimental and may not progress if deemed uninterpretable.