Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for 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
Effective Date	:	[20-Nov-2017]

Description:

- The purpose of this RAP is to describe the planned analyses and outputs that will be reported by GSK Clinical Statistics & Programming Department.
- This RAP is to describe Part A only since the study was terminated early and Part B was cancelled prior to the completion of Part A; however, Part A was completed as planned.
- Analyses that will be performed by Massachusetts General Hospital (MGH)/Health Science & Technology (HST) Athinoula A. Martinos Center for Biomedical Imaging [Martinos] are described separately and are provide in Attachment 11.

Author's Name and Functional Area:

PPD Principle Statistician (Clinical Statistics)	20-Nov-2017

Approved by:

PPD Director (Clinical Statistics)	30-Nov-2017

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this RAP is to describe the planned analyses and outputs that will be reported by GSK Clinical Statistics & Programming Department. At the time of the RAP preparation, the study had terminated early and Part B was cancelled prior to the completion of Part A; however, Part A was completed as planned. This RAP is for Part A only. • Analysis that will be performed by Massachusetts General Hospital (MGH)/Health Science & Technology (HST) Athinoula A. Martinos Center for Biomedical Imaging [Martinos] is described in a separate document added as Attachment 11 to this RAP.
Protocol	• This RAP is based on protocol amendment 1 [(Dated: 28/Nov/2016) of study GSK 201840 (GSK Document No.: 2015N250344_02] and eCRF Version 5.1.
Primary Objective	• 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
Primary Endpoints	• 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)
Study 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.
Planned Analyses	• Analysis of primary and some secondary endpoints for Part A will be performed by Martinos. Details are described in Attachment 11.
Analysis Populations	• For this study, the analysis set will include subjects who have valid data as determined at the discretion by the imaging laboratory.
Hypothesis	• No primary hypothesis was pre-specified due to the exploratory nature of the study.
Primary Analyses	• The primary analyses will be exploratory in nature and will consist of summary outputs and listings and will cover the following primary endpoints: 1. Resting-state BOLD signal (fMRI) 2. Regional cerebral blood flow (rCBF) (fMRI-ASL) 3. Glutamate concentration in nausea-associated brain regions (Magnetic resonance spectroscopy (MRS))

Overview	Key Elements of the RAP
	4. GABA concentration in nausea-associated brain regions (MRS)
Secondary Analyses	• Secondary analyses will also be exploratory in nature and will consist of summary statistics and listings for the following endpoints: 1. Heart rate** 2. heart rate variability** 3. respiratory rate** 4. ECG intervals** 5. blood pressure** 6. skin conductance level** • Secondary analyses consisting of summary statistics for continuous variables and frequency and percent for categorical variables will be performed for the following safety endpoints: 1. Vital signs 2. clinical laboratory tests* 3. adverse events 4. Nausea ratings scale ** 5. Gastrointestinal-Visual analogue scale (GI VAS) 6. Motion Sickness Assessment Questionnaire (MSAQ) *Only listings will be provided. ** Will be provided by Martinos

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

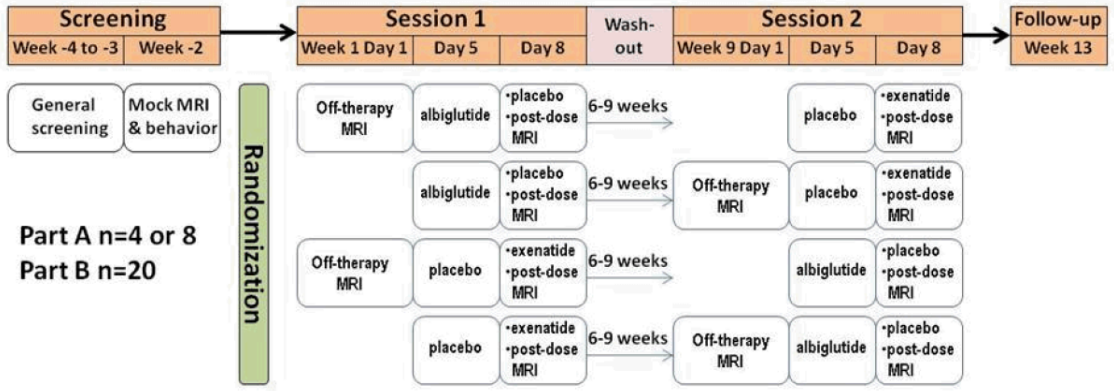
Since the study was terminated early; Part B was cancelled prior to the completion of Part A, 4 subjects completed Part A as planned and a decision was made to not complete group analysis of the 4 subjects. Therefore, no interim analyses will be performed as stated in the originally planned statistical analysis specified in the protocol / protocol amendment 1 [(Dated: 28/Nov/2016)].

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To explore the effect of single dose 50 mg albiglutide compared to single dose 10 g 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 Objectives	**Secondary Endpoints**
• To evaluate autonomic effects of single dose 50 mg albiglutide compared to single dose 10 g exenatide	• Heart rate, heart rate variability, respiratory rate, ECG intervals, blood pressure, skin conductance level
• To assess safety and tolerability of single dose 50 mg albiglutide and single dose 10 g exenatide	• Vital signs, clinical laboratory tests, adverse events, Nausea ratings scale, GI VAS, and MSAQ
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate gastric myoelectrical activity (GMA) of single dose 50 mg albiglutide compared to single dose10 g 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. (Martinos will provide analysis data if considered valid)

2.3. Study Design

Overview of Study Design and Key Features



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

Design Features	• 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
Treatment Assignment & Dosing	• 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

Interim Analysis	• Originally there were 2 potential interim data reviews during the study. However, since the study was terminated early no interim data review will be performed.
Final Analysis	• Final analysis will be performed after data from all randomized subjects in Part A have been cleaned and locked.

2.4. Statistical Hypotheses

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

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analyses will be performed since the study was terminated early and Part B cancelled prior to the completion of Part A; however, Part A was completed as planned.

3.2. Final Analyses

The final reporting will be performed after the completion of the following sequential steps:

1. All subjects have completed Part A of the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared.

The reporting and analysis of imaging data after completion of the study will be performed by Martinos. Details are described in Attachment 11.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Screened	• All participants who were screened will be considered for this population. This population will be used for summarizing screening status	• Screen failure
Enrolled	• All participants who were successfully screened and enrolled for the trial and for whom a record exists on the study database.	• Study population
Safety	• Comprise of all subjects who receive at least one dose of study treatment. • This population will be based on the treatment the subject actually received. • This population will include subjects who were replaced due to imaging data being invalid or not evaluable but received study drug.	• Safety
Analysis Set (Randomised)	• Comprise of all randomized subjects who receive treatment and with valid imaging data, that will be determined by Martinos. • Subjects who are replaced are excluded from this population.	• Imaging (Mechanism of Action)

NOTES :

- Please refer to Appendix 7: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be reviewed and tracked throughout the conduct of the study. However, there is no per-protocol analysis that will be performed for this study.

  Only listings of the Protocol deviations will be provided if any.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Imaging Analysis Population
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Values of Potential Clinical Importance
Error! Reference source not found.	**Error! Reference source not found.**: Data Display Standards & Handling Conventions
Error! Reference source not found.	**Error! Reference source not found.**: Abbreviations & Trade Marks
Error! Reference source not found.	**Error! Reference source not found.**: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population summary will be based on the Safety population, unless otherwise specified.

Subject characteristics and safety data (captured in the eCRF) will be reported by GSK. GSK Statistics & Programming (S&P) will provide summary tables data listings of subject characteristics and safety data for Part A.

Table 2 provides an overview of the planned study population summaries, with full details of data displays being presented in Appendix 7: List of Data Displays.

Table 2 Overview of Planned Study Population Summaries

[Endpoint / Parameter / Display Type]	Data Displays Generated		
	Table	Figure	Listing
Part A			
Reasons for Screening Failures	Y		Y
Randomization			Y
Subject Disposition	Y		Y
Summary of Number of Subjects by Site ID	Y		
Demographics and Baseline Characteristics	Y		Y
Race (& Racial Combinations)	Y		Y
Age Ranges	Y		
Medical Condition & Concomitant Medications			
Medical History			Y
Concomitant Medication			Y
Exposure			
Exposure to Study Drug			Y

NOTES :

- Y = Yes display generated.

6.2. Demographic and Baseline Characteristics

Continuous variables such as age, body mass index, weight, and height will be summarized using descriptive statistics (n, mean, standard deviation, and median, minimum, maximum). Categorical variables including sex, race, ethnicity, tobacco use, alcohol intake, caffeine intake, and baseline weight category (<90 kg or ≥90 kg) will be summarized using numbers and percentages.
Continuous variables such as age, body mass index, weight, and height will be presented in a by-subject listing. Listings will be presented using the safety population.

6.3. Exposure to Study Drug

A by-subject listing of study drug administration will also be presented.

6.4. Medications

Any prior and concomitant medication used during the study will be recorded and coded using GSKDrug Dictionary (GSKDRUG), which will be updated whenever available throughout the life of the study.

Any medication used during the study will be recorded, which will be updated whenever available throughout the life of the study.

All medications will be listed.

7. PRIMARY STATISTICAL ANALYSES

The imaging data will be reported by Martinos at the end of the study. Details of the planned analyses are described in Attachment 11.

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the all randomised population, unless otherwise specified.

The efficacy analyses will be performed by Martinos, details of the planned analysed are described in Attachment 11.

8. SECONDARY STATISTICAL ANALYSES

8.1. Secondary Efficacy Analyses

The secondary analysis to list autonomic effects of albiglutide compared to exenatide will be performed and reported by Martinos. Details of the planned analyses are described in Attachment 11.

8.2. Safety & Tolerability Analyses

8.2.1. Overview of Planned Analyses

The safety analyses will be based on the Safety population, unless otherwise specified.

Safety data (captured in the eCRF) will be reported by GSK. GSK Statistics & Programming (S&P) will provide summary tables and data listings of safety data for Part A data.

Table provides an overview of the planned analyses, with further details of data displays being presented in Appendix 7: List of Data Displays.

Table 3 Overview of Planned Safety & Tolerability Analyses

[Endpoint / Parameter/ Display Type]	Data Displays Generated			
	Summary		Individual	
	Table	Figure	Figure	Listing
Vital Signs	Y			Y
Clinical Laboratory*				Y
Adverse Events	Y			Y
12-lead ECG				Y
GI- VAS	Y			Y
MSAQ	Y			Y
MRI				Y

*Clinical Laboratory will include Fasting Plasma Glucose.

8.2.2. Vital Signs

The vital sign summary and analysis will include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and heart rate (bpm).

For Part A, each vital sign parameter at every scheduled assessment time point will be summarized using descriptive statistics. Additionally, the number of subjects with vital signs of potential clinical concern will also be summarized. The criteria for vital signs of potential clinical concern are detailed in Appendix 7: Values of Potential Clinical Importance.

All summaries will be done for the safety population and all vital sign data will be listed.

8.2.3. Clinical Laboratory Evaluations

Laboratory parameters include the following tests: hematology, chemistry and urinalysis. Established or generally acknowledged methods, normal ranges, and quality control procedures will be supplied by Quest Diagnostics Clinical Laboratory for the study records.

All laboratory parameters as collected will be presented in by-subject listings at every scheduled assessment time point for the safety population.

Additionally, listing of the number of subjects with laboratory values of potential clinical concern will be provided and scheduled assessment time point for hematology and chemistry. The criteria for laboratory values of potential clinical concern are detailed in Appendix 7: Values of Potential Clinical Importance.

Listings of clinical laboratory evaluations will be provided.

8.2.4. Adverse Events

All AEs will be coded using MedDRA which will be updated whenever available throughout the life of the study.

For Part A safety review, adverse events will be summarized by treatment group. Summary of the number and percentage of subjects with any AE and the total number of AEs recorded will be provided. SAEs will be summarized.

All AEs will be listed in a subject data listing.

8.2.5. Most Common Adverse Events

A summary of most common adverse events (>2% total incidence in any treatment arm) by treatment will be produced.

8.2.6. Deaths and Serious Adverse Events

Deaths and serious adverse events will be listed.

8.2.7. Nausea Rating Scale

Nausea rating scale will be provided by Martinos.

8.2.8. GI VAS

Summary statistics outputs and listings for GI VAS will be provided

8.2.9. MSAQ

Summary statistics outputs and listing for MSAQ will be provided.

8.2.10. Pregnancies

Listings for Pregnancies will be produced if any.

9. REFERENCES

None.

10. APPENDICES

Section	Appendix
Section 10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
Section 10.2	Appendix 2: Time and Events
Section 10.3	Appendix 3: Assessment Windows
Section 10.4	Appendix 4: Values of Potential Clinical Importance
Section **Error! Reference source not found.**	**Error! Reference source not found.**: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors
Section 10.6	Appendix 6: Abbreviations & Trade Marks
Section 10.7	Appendix 7: List of Data Displays

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per-Protocol Population

The Protocol Deviation Management Plan (21/Feb/2017) will be used to identify the important protocol deviations. It is intended to categorize important protocol deviations that are anticipated to occur in a study and to document study-specific requirements for cross-functional team review of these protocol deviations and other deviations that may occur in the study. There is no pre-defined per protocol population criteria.

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

Procedure	Screening		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 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	
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	Screening		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 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[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.

Note: reference to Table 2 in footnote e is in the protocol.

10.3. Appendix 3: Assessment Windows

10.3.1. Definitions of Study Day

When study day is used for display or in comparisons the following algorithm will be used:

- Study day = date of assessment – date of first dose + 1, if day of assessment >= first dose date
- Study day = date of assessment – date of first dose, if day of assessment < first dose date

Note that the date of first dose is Day 1 and the day before the date of first dose is Day -1 (there is no Day 0).

10.4. Appendix 4: Values of Potential Clinical Importance

10.4.1. Laboratory

Hematology			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
Basophils	GI/L	None	None
Eosinophils	GI/L	None	None
Hematocrit	1	>0.1 decrease	>0.05 below LLN >0.04 above ULN
Hemoglobin	g/L	>25 g/L decrease	>20 g/L below LLN >10 g/L above ULN
Lymphocytes	GI/L	None	<0.5 x LLN
Monocytes	GI/L	None	None
Neutrophils	GI/L	None	<1 GI/L
Neutrophil Bands	GI/L	None	None
Platelets	GI/L	None	<80 GI/L >500 GI/L
Red Blood Cell Count	TI/L	None	None
Segmented Neutrophils	GI/L	None	<0.5 x LLN
White Blood Cell Count	GI/L	None	>1 GI/L below LLN >5 GI/L above ULN

Chemistry			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
Albumin	g/L	None	>5 g/L above ULN or below LLN
Alkaline Phosphatase	U/L	None	>3 x ULN
ALT	U/L	None	>3 x ULN
AST	U/L	None	>3 x ULN
Bicarbonate (Carbon Dioxide Content)	mmol/L	None	<16 mmol/L > 40 mmol/L
Blood Urea	mmol/L	None	>2 x ULN

Chemistry			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
Nitrogen			
Calcitonin	pmol/L	None	>100
Calcium	mmol/L	None	<1.8 mmol/L >3.0 mmol/L
Chloride	mmol/L	None	None
Creatinine	umol/L	None	>159 umol/L
Direct Bilirubin	umol/L	None	>1.35 x ULN
Gamma Glutamyl Transferase	U/L	None	>3 x ULN
Glucose (fasting)	mmol/L	None	<3 mmol/L >22 mmol/L
Potassium	mmol/L	None	>0.5 mmol/L below LLN >1.0 mmol/L above ULN
Sodium	mmol/L	None	>5 mmol/L above ULN or below LLN
Total Bilirubin	umol/L	None	>1.5 x ULN
Total Protein	g/L	None	>15 g/L above ULN or below LLN
Uric acid	umol/L	None	>654 umol/L
Free Fatty Acids	mmol/L	None	None
HDL Cholesterol	mmol/L	None	None
LDL Cholesterol	mmol/L	None	None
Triglycerides	mmol/L	None	> 9.04 mmol/L
Total Cholesterol	mmol/L	None	None

Liver Function Tests	
Laboratory Test	**Potential Clinical Concern Value**
ALT	≥ 2 x ULN ≥ 3 x ULN ≥ 5 x ULN ≥ 8 x ULN ≥ 10 x ULN ≥ 3 x ULN and Total Bilirubin ≥ 2 x ULN
AST	≥ 2 x ULN ≥ 3 x ULN ≥ 5 x ULN ≥ 8 x ULN ≥ 10 x ULN ≥ 3 x ULN and Total Bilirubin ≥ 2 x ULN
Total Bilirubin	≥ 1.5 x ULN ≥ 2 x ULN ≥ 3 x ULN ≥ 5 x ULN ≥ 8 x ULN ≥ 10 x ULN

10.4.2. Vital Signs

Parameter	Units	Potential Clinical Concern Value
Systolic BP	mmHg	<100 mmHg >170 mmHg
Diastolic BP	mmHg	<50 mmHg >110 mmHg
Heart rate	bpm	<50 bpm > 120 bpm

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment Display Descriptors

The study treatment descriptors are shown below.

Treatment Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Albiglutide 50mg	Albiglutide 50mg	1
E	Exenatide 10mcg	Exenatide 10mcg	2

10.6. Appendix 6 – Abbreviations & Trade Marks

10.6.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
BOLD	Blood oxygen Level dependent
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
fMRI	Functional magnetic resonance imaging
GABA	Gama-aminobutyric acid
GI-VAS	Gastrointestinal-Visual analogue scale
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
LOC	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
MRS	Magnetic resonance spectroscopy
MSAQ	Motion Sickness Assessment Questionnaire
PCASL	Pseudo-Continuous ASL
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan

Abbreviation	Description
RAMOS	Randomization & Medication Ordering System
rCBF	Regional cerebral blood flow
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
GSK	GlaxoSmithKline

10.6.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
MedDRA

10.7. Appendix 7: List of Data Displays

10.7.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.8	NA
Efficacy*		
Safety	3.1 to 3.5	NA
Section	**Listings**	
ICH Listings	1 to 21	
Other Listings	22 to 24	

*Will be provided by Martinos

10.7.2. Study Population Tables

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1A	Summary of Subject Disposition for the Subject Conclusion Record		SAC
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures		SAC
Demography					
1.3.	Safety	DM1	Summary of Demographic Characteristics		SAC
1.4.	Enrolled	DM11	Summary of Age Ranges		SAC
1.5.	Safety	DM5	Summary of Race and Racial Combinations		SAC
1.6.	Safety	DM6	Summary of Race and Racial Combination Details		SAC
1.7.	Enrolled	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		SAC
1.8.	Enrolled	SP1A	Summary of Study Population		SAC

10.7.3. Efficacy Tables

All Efficacy tables and listings will be provided by Martinos.

10.7.4. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.1.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.2.	Safety	AE15	Summary of Common (>=2%) non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.3.	Safety		Vital Signs of Clinical Concern by Visit		SAC
3.4.	Safety		Summary of GI- VAS		SAC
3.5.	Safety		Summary of MSAQ		SAC

10.7.5. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1	Safety	CP_TA1	Listing of Randomised and Actual Treatments		SAC
2	Safety	ES3	Listing of Reasons for Study Withdrawal		SAC
3	All Screened	ES7	Listing of Reasons for Screening Failure		SAC
4	Enrolled	SA3a	Listing of Subjects Excluded from Any Populations		SAC
5	Safety	DV2	Listing of Important Protocol Deviations		SAC
6	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
7	Safety	DM2	Listing of Demographic Characteristics		SAC
8	Safety	DM10	Listing of Race		SAC
9	Safety	EX3	Listing of Exposure		SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
10	Safety	AE7	Listings of Subject Numbers for Individual Adverse Events		SAC
11	Safety	AE9	Listing of All Adverse Events		SAC
12	Safety	AE9	Listing of Serious Adverse Events		SAC
13	Safety	AE9	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		SAC
14	Safety	AE7	Listing of subjects who withdrew from study due to Adverse Event		SAC
15	Safety	LB5	Listing of Clinical Chemistry Laboratory Data for Subjects Abnormalities of Potential Clinical Importance		SAC
16	Safety	LB5	Listing of Haematology Data for Subjects with Abnormalities of Potential Clinical Importance		SAC
17	Safety	UR2b	Listing of Urinalysis Data		SAC
18	Safety	EG3	Listing of 12 lead ECG Values		SAC
19	Safety	CP_VS4	Listing of Vital Signs for Subjects with Abnormalities of Potential Clinical Importance		SAC
20	Safety	LB5	Listing of all Haematology Data		SAC
21	Safety	LB5	Listing of all Chemistry Data		SAC

10.7.6. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
22	Analysis		Listing of GI- VAS		SAC
23	Analysis		Listing of MSAQ		SAC
24	Analysis		Listing of MRI		SAC

11. ATTACHMENTS [DOCUMENTATION FROM MARTINOS]

11.1. Reporting & Analysis Plan for Imaging Data for Part A

11.1.1. Overview of Quality Control for Imaging Data

Quality control procedures will include visual inspection of raw brain images for presence of various artifacts, including but not limited to, aliasing, excessive distortion, Nyquist N/2 ghosting, and signal inhomogeneities. We will also assess head motion correction parameters to ensure that subjects were not moving excessively during the functional MRI (BOLD fMRI and pCASL) scans. We will evaluate 1) total translation and rotation motion, 2) relative TR-to-TR motion, 3) number of relative translations (> 0.1 mm). For pCASL data, we will calculate rCBF and ensure values within the gray matter are within normal bounds (40-60 mm/100 g tissue/min). For ^{1}H-MRS data we will assess spectra to ensure adequate SNR (Cramer–Rao lower bounds values below 40%).

We will perform single-subject level analyses and include data from (1) resting-state BOLD fMRI, (2) pseudo-continuous arterial spin labelling (pCASL), and (3) proton-density weighted magnetic resonance spectroscopy (^{1}H-MRS).

Primary Outcomes/Endpoints:

1. Resting-state functional connectivity (resting-state BOLD fMRI)
2. Regional cerebral blood flow (rCBF) (pCASL)
3. Glutamine/Glutamate (Glx) and GABA concentrations (^{1}H-MRS)

1. Resting-state fMRI (rs-fMRI)

Resting-state BOLD signal MRI data collected at off-therapy and exenatide post-dose MRI scan sessions will be analyzed using a whole-brain seed-to-voxel approach. The seed-to-voxel driven approach will include *a priori* seed ROIs placed in brain areas subserving nausea-related processing including regions identified from our prior study (Napadow et al. Cereb Ctx 2013). These regions will include: interoceptive/sensory (insula, dACC), emotional/affective (amygdala, pgACC), and cognitive/evaluative (dlPFC/OFC) brain areas, primary visual (V1) and extrastriate cortices (area MT+/V5). Group analyses will be performed using a paired t-test (off-therapy vs. exenatide) with FSL's FLAME (FMRIB's Local Analysis of Mixed Effects).

2. pCASL

pCASL data will be analysed to assess regional cerebral blood flow (rCBF) within the brain during off-therapy relative to exenatide post-dose MRI scans. Quality control of imaging data will be performed by visual inspection with adequate data denoted by mean rCBF values over the gray matter within a previously defined normal range (i.e., 40-60 mm/100 g tissue/min). In addition, all data will undergo motion and physiological noise

correction. These rCBF maps will be calculated for each subject and each scan at the single subject-level.

3. ^{1}H-MRS

Magnetic resonance spectroscopy (^{1}H-MRS) analysis will assess regional differences in glutamine/glutamate (Glx) and GABA concentrations, normalized as a ratio with creatine. MRS quantification of metabolites of interest will be based on frequency domain analysis using a Linear Combination of Model spectra (LCModel). Cramer–Rao lower bounds (CRLBs), as reported from the LCModel analysis, will be used to assess the reliability of the major metabolites and adequate SNR. CRLBs values less than 40% will be further analyzed. Metabolite maps for each subject, and each session will be calculated.

Secondary outcomes/endpoints:
Additional analyses will be conducted for secondary outcome measures including heart rate, heart rate variability, respiratory rate, ECG intervals, blood pressure, and skin conductance level. Electrogastrogram (EGG) data will also be analysed as a secondary exploratory outcome. We will provide clean, processed physiological data in the subject/scan directories when available (secondary ANS data will not be available from every scan due to MR-induced artifacts).