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

Title	:	Reporting and Analysis Plan for A Randomized, Open-label, Active-Controlled, Parallel-Group, Exploratory Study on the Effects of Repeated Doses of Albiglutide compared to Exenatide on Gastric Myoelectrical Activity and Gastric Emptying in Subjects with Type 2 Diabetes Mellitus
Compound Number	:	GSK716155
Effective Date	:	17-Aug-2017
Amendment	:	01

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204879.
- This RAP is intended to describe the exploratory endpoints for the study Part A only.
- This study is terminated early prior to completion of Part A with a limited number of subjects (N=4) enrolled. Therefore, a synoptic CSR is planned and a brief RAP document is prepared accordingly.
- This RAP will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) Deliverable.

Revision Chronology

GlaxoSmithKline Document	Date	Version
Reporting and Analysis Plan (RAP)204879_Final	23-Jun-2017	Original
Reporting and Analysis Plan (RAP)204879_Amendment_Final_01	17-Aug-2017	Amendment No. 1

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

- Appendix 5 Section 9.5.1 Data Display Numbering is updated with the appropriate listing number.
- Appendix 5 Section 9.53 added 5 listing below:

  Listing 15: Listing of Exposure Data

  Listing 17: Listing of Visual Analogue Scale (VAS) Scores (0-100mm scale)

  Listing 18: Listing of Gastric Emptying 13C Excreted in Breath (kPCD1) Over Time by Treatment and Visit

  Listing 19: Listing of Time to Half Gastric Emptying (GET1/2) by Visit

  Listing 20: Listing of Volume of Water Ingested during EGG with Water Load Test

  And Listing of all EGG Endpoints the listing number changed from 15 to 16

Author's Name and Functional Area:

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Purpose	To gain insight into a potential peripheral mechanism of nausea associated with glucagon-like peptide-1 receptor (GLP-1R) agonists; this study will compare the effect of albiglutide and exenatide on gastric myoelectrical activity (GMA), gastric emptying (GE) and nausea [as measured by visual analogue scale (VAS)] in subjects with type 2 diabetes mellitus (T2DM). The study is divided in two parts. Part A will characterize the GMA, GE and nausea response to exenatide and confirm exenatide as a positive control for Part B. At the time the RAP preparation, the study had terminated early with a limited number of subjects enrolled in Part A.
Protocol	• This RAP is based on the protocol amendment 1 [(Dated: 23/June/2016) of study GSK 204879 (GSK Document No. : 2015N255772_01) and eCRF Version 1.
Primary Objective	To evaluate the effect of exenatide on GMA (pilot phase).
Primary Endpoint	(All endpoints for Part A are exploratory) • Change from baseline of electrogastrogram (EGG) parameters at each recording time interval (pre-and 10, 20 and 30 min after water load) compared to baseline: o Distribution of average power by frequency region (as % of power) o Ratios of average power post- WLT/pre-WLT by frequency region o Percentage (%) of time with the dominant EGG frequencies in the four frequency ranges (bradygastria, normal, tachygastria and duodenal) • Change from baseline EGG parameters related to VAS of nausea at each recording time interval (pre-and 10, 20 and 30 min after water load) at Day 4
Study Design	• This is a single arm, open label pilot phase to evaluate the effect of 5-day repeated doses of exenatide (10 µg twice daily) on GMA, GE and nausea in subjects with T2DM. • The study will comprise 3 study periods: screening/wash-out (up to 3 weeks), treatment (5 days), and post-treatment follow-up (within 7 days after the last dose of exenatide). • The study will recruit subjects with T2DM (>6 months since diagnosis) with glycated hemoglobin (HbA1c) >6.5% and ≤9.0%, fasting plasma glucose (FPG) <=210 mg/dL (central lab) at screening and on a current regimen of diet and exercise or a stable dose of one oral anti-diabetic medication (OAM) (maintained for >= 2 months prior to screening). • Fasting capillary blood glucose will be confirmed to be <=230 mg/dL at baseline. • Subjects receiving monotherapy with an OAM of metformin,

	sulfonylurea, sodium glucose co-transporter-2 (SGLT2) inhibitors, or meglitinide at screening will be washed out for 2 days for immediate release and 4 days for extended release OAM prior to baseline. • Subject's nutritional plan will be optimized prior to baseline and maintained during the entire study. • All evaluations and assessments will be performed as outpatient visits. Subjects will undergo 2 EGG and 2 gastric emptying breath tests (GEBT) assessments. • At the end of the Part A, subjects previously on an OAM will restart OAM at the discretion of the investigator after the last dose of exenatide. The half-life of exenatide (2-3 hours) should be taken into consideration. • The total duration of a subject's participation will be approximately 5 weeks.
Planned Analyses	• **Part A**: Final Analysis: After at least 10 evaluable subjects defined as having at least one valid pre-dose EGG and one valid post –dose EGG , the final analysis for the clinical study report will be performed. At this time, the database will be frozen. The study is terminated early with a limited number of subjects enrolled in Part A.
Analysis Populations	The analysis set will include subjects who have taken at least one dose of study medication and one valid EGG data. Data will be assessed and reviewed by the central reader before it is considered valid.
Hypothesis	No formal statistical hypotheses are being tested in Part A. Part A will be a pilot phase investigating the effect of repeated doses of exenatide on GMA, GE, and VAS of nausea.
Primary Analyses	No formal statistical analyses will be performed for the exploratory endpoints for Part A. All exploratory endpoints will be assessed using descriptive statistics and graphical displays as appropriate.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

The study terminated early with a limited number of subjects enrolled in Part A. Therefore, only data listings will be produced for selected data. These are limited in scope compared to the originally planned statistical analysis specified in the protocol amendment 1 [(Dated: June 23, 2016)].

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

Part A:

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the effect of exenatide on GMA	• Change from baseline of EGG parameters at each recording time interval (pre-and 10, 20 and 30 min after water load) compared to baseline: o Distribution of average power by frequency region (as % of power) o Ratios of average power post- WLT/pre-WLT by frequency region o Percentage (%) of time with the dominant EGG frequencies in the four frequency ranges (bradygastria, normal, tachygastria and duodenal) • Change from baseline EGG parameters related to VAS of nausea at each recording time interval (pre-and 10, 20 and 30 min after water load) at Day 4
To assess the effect of exenatide on GE	• Change from baseline of time to half gastric emptying (GEt½) at Day 5 • Change from baseline of profiles of 13C excreted in breath (kPCD1) at Day 5 and at each time interval (45, 90, 120, 150, 180 and 240 min).
To assess the volume of water ingested during EGG	Change from baseline of volume of water ingested during EGG with water load test at Day 4.
To evaluate the effect of exenatide on stomach fullness, hunger, bloating and abdominal pain during EGG with water load test	Change from baseline of VAS of stomach fullness, hunger, bloating and abdominal pain during the EGG water load test at each time interval (pre-and 10, 20 and 30 min after water load) at Day 4
To evaluate safety and tolerability of exenatide	• Vital signs, clinical laboratory tests, AEs, and GCSI-DD. • Nausea AEs presenting outside the timing of the WLT and GCSI-DD.

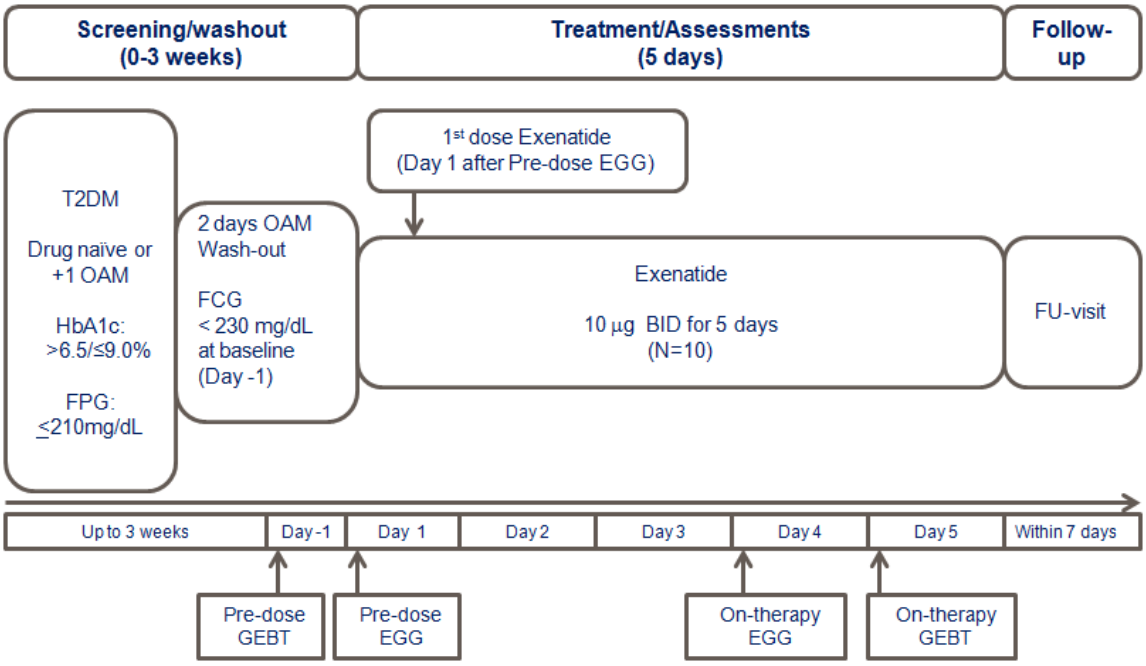
Objectives	Endpoints
To evaluate change in gastric rhythm status (Data permitting)	At Day 4; over 30 min and at each time interval (pre-and 10, 20 and 30 min after • water load). • Number and % of subjects with a shift in gastric rhythm status. • Number and % of subjects by gastric rhythm status at each time interval. • Mean and mean change from baseline in • average dominant frequency

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

2.3. Study Design

2.3.1. Overview of Study Design and Key Features

Overview of Study Design and Key Features Part A



Design Features	Part A is a single arm, open label pilot phase 5-days of treatment.
Dosing	All subjects will receive 10 µg subcutaneous exenatide twice daily for 5 days. The total duration of a subject's participation will be approximately 5 weeks.
Interim Analysis	No interim analysis is planned for this study.

Due to early termination the entirety of the study conduct was not carried out.

2.3.2. Study Design

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

At the time the RAP is being prepared, the study is terminated early with a limited number of subjects enrolled in Part A.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned for this study.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential step:

1. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Part A: Pharmacodynamic	Comprise of all subjects who have taken at least one dose of study medication and one valid EGG data Data will be assessed and reviewed by the central reader before it is considered valid. The central reader will provide the valid data that will be used for the analyses.	Pharmacodynamic
All Subjects	All subjects with at least one dose of study medication.	Safety
Enrolled	All enrolled subjects.	Enrolled

NOTES :

- Please refer to Appendix 5: List of Data Displays which details the population to be used for each displays being generated.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Reporting Conventions

- All data displays will be presented according to the Integrated Data Standards Library (IDSL) reporting standards, where applicable.
- Analyses will be performed using the 9.1.3 version of the SAS System or higher (SAS is a registered trademark of the SAS Institute Inc., Cary, NC, USA). Programs will be imported into HARP and the final output will be produced by running drivers in HARP.
- Data collected at unplanned (i.e. unscheduled) time points will not be included in the summaries by visit unless otherwise stated. Unscheduled or unplanned readings will be presented in the listings and they will be included when determining worst-case flagging for post-baseline summaries.
- In all data displays, planned and actual relative times will be relative to the study drug dosing time of the relevant dosing session.
- Refer to IDSL standards (when applicable) for decimal place conventions. Raw data will generally be presented to the same number of decimal places as it was collected.
- All data will be reported according to the actual treatment the subject received. Any departures from the planned treatment according to the randomization schedule will be documented in the report.
- All observations that occurred prior to dosing will be considered as part of the pre-dose period. All observations that occur during dosing will be attributed to the subject's treatment.

Deviations from the analyses in the RAP will be identified in the final clinical study report.

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
9.1	Appendix 1: Time & Events
9.2	Appendix 2: Assessment Windows
9.3	Appendix 3: Values of Potential Clinical Importance
9.4	Appendix 4: Abbreviations and Trademarks
9.5	Appendix 5: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 5: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated		
	Figure	Table	Listing
Subject Disposition			
Reasons for Withdrawal from Study		Y	Y
Demography and Baseline Characteristics			
Demographics and Baseline Characteristics		Y	Y
Race & Racial Combinations		Y	Y
Number of subjects by Site ID		Y	Y
Age Ranges		Y	
Medical Condition & Concomitant Medications			
Concomitant Medication			Y
Exposure			
Exposure to Study Drug			Y

Note: additional tables, listings and figures will be provided in Appendix 5: List of Data Displays.

- Y = Yes display generated.

Following review of the data, additional analyses maybe conducted to further support the evaluation and interpretation of the data.

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, 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, if appropriate.

6.3. Exposure to Study Drug

A by-subject listing of study drug administration will also be presented. Overall study drug administration and treatment compliance will be present with the exposure to study drug listing.

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.

6.5. Safety Analyses

6.5.1. Overview of Planned Analyses

The safety analyses will be based on all subjects' population.

Table 3 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 5: List of Data Displays.

Table 3 Overview of Planned Safety Analyses

Endpoints	Observed				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Adverse Events	**Y**			Y				
Clinical Laboratory				Y				
Vital Signs				Y				
GCSI-DD				Y				

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

Following review of the data, additional analyses maybe conducted to further support the evaluation and interpretation of the data.

6.5.2. Adverse Events

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

All AEs will be listed in a subject data listing.

6.5.3. Clinical Laboratory Evaluations

6.5.3.1. Chemistry, Hematology and Urinalysis

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 central lab for the study records.

Hematology parameters include red blood count, hemoglobin, hematocrit white blood cell count with differential, and platelet count. Chemistry blood urea nitrogen (BUN), potassium, aspartate aminotransferase (AST), total and direct bilirubin, creatinine, sodium, ALT, total protein, calcium, magnesium, chloride, phosphorus albumin, gamma glutamyl transferase (GGT), estimated glomerular filtration rate (eGFR), and lipids

(including total cholesterol, LDL-C, HDL C, triglycerides,). Urinalysis parameters include microalbumin and creatnine and specific gravity, pH, glucose, nitrates, leukocytes esterase, blood and ketones by dipstick and microscopic examination (if blood or protein is abnormal).

All laboratory parameters as collected will be presented in by-subject listings at every scheduled assessment time point. All listings will be done for the safety population and all laboratory data will be listed including other laboratory tests, such as TSH, and urine pregnancy test results.

Additionally, the number of subjects with laboratory values of potential clinical concern will be provided in a listing by treatment group and scheduled assessment time point for hematology and chemistry. The criteria for laboratory values of potential clinical concern are detailed in Appendix 3: Values of Potential Clinical Importance.

A listing of laboratory values of potential clinical concern will be provided for liver function tests, including ALT, AST, and total bilirubin. The criteria for liver function tests of potential clinical concern are detailed in Appendix 3: Values of Potential Clinical Importance.

6.5.4. Vital Signs

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

Each vital sign parameter at every scheduled assessment time point will be presented in by-subject listings. .

All listings will be produced for all subjects population.

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

The GCSI-DD consists of nine symptom severity items covering the following domains: nausea/vomiting; fullness/early satiety, and bloating. In addition, the GCSI-DD contains two symptom severity items upper abdominal pain and overall rating of gastroparesis symptoms. Patients rate each symptom on a 6-point scale from 0 – 5 with lower scores representing less symptom severity. All questions addressed in the GCSI-DD and the overall severity question will be listed in a subject data listing and by time point.

7. OTHER STATISTICAL ANALYSES (EXPLORATORY)

7.1. Overview of Planned Analyses

The study was terminated early and therefore no analysis will be performed but data listing will be generated for all exploratory endpoints as in Appendix 5.

7.2. Exploratory Analyses

Listing will be provided for all endpoints.

8. REFERENCES

None.

9. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 9.1	Appendix 1: Time and Events
Section 9.2	Appendix 2: Assessment Windows
Section 9.3	Appendix 3: Values of Potential Clinical Importance
Section 9.4	Appendix 4: Abbreviations & Trade Marks
Section 9.5	Appendix 5: List of Data Displays

9.1. Appendix 1: Time & Events

9.1.1. Protocol Defined Time & Events Part A

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

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

1. **Before baseline assessment (Day -1)**, the investigator must review **all** inclusion and exclusion criteria to confirm subject's eligibility. If a subject no longer meets all of the eligibility criteria, **do not administer the study treatment** and contact the Medical Monitor to discuss how to proceed (e.g., to determine if repeat testing is warranted).
2. For subjects taking OAM at screening only. At a minimum, two day washout for immediate release and at minimum 4 day washout for extended release OAMs. See footnote 13. For information on restarting OAM refer to Section 6.9.
3. A small meal will be provided 2 hrs prior to the EGG procedure (Section 7.3.1). A meal will also be provided post-procedure for both the EGG and GEBT.
4. Details of full and brief physical examinations are provided in Section 7.4.3.
5. SAEs related to study participation only.
6. The GCSI-DD questionnaire will be completed after the standard AE questions have been answered.
7. Clinical chemistry, hematology, urinalysis and lipid assessments are described in Section 7.4.6. Lipids will be assessed at screening only.
8. Fasting capillary glucose will be measured prior to administration of exenatide. On GEBT (Day 5) or EGG (Day 1 and Day 4) assessment days, fasting capillary glucose will be measured prior to the GEBT or EGG procedure.
9. Subjects will be provided with diet and exercise guidance (see Section 7.4.8) and instructed on self monitoring blood glucose at screening (See Section 7.4.9). Subject will be instructed to bring in their glucometers at each visit for review. Diet/exercise/SMBG reinforced at subsequent visits.
10. Informed consent for optional genetic research should be obtained before collecting a sample.
11. On the morning of Day 1, subjects will receive instructions and training on exenatide self administration and will be monitored by medical staff at the clinic during administration of the first dose. The first dose of exenatide will be administered after the baseline EGG procedure and before the post-procedure meal.
12. On Day 4 and 5, the morning dose of exenatide will be administered at clinic 1 hr (±15 min) before the EGG or GEBT procedure.
13. Every effort should be made to schedule the procedures on the nominal visit day identified. However, in order to meet scheduling needs, subjects taking OAM can schedule Day-1 up to 3 days prior to Day 1 and the OAM stopped at least the day before the GEBT . For subjects treated with diet and exercise alone Day-1 can occur within 7 days prior to Day 1. The EGG and GEBT should not be scheduled on the same day

Note: section noted in time and event table referring to the protocol.

9.2. Appendix 2: Assessment Windows

9.2.1. 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).

9.3. Appendix 3: Values of Potential Clinical Importance

9.3.1. 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 Nitrogen	mmol/L	None	>2 x ULN
Calcitonin	pmol/L	None	>100
Calcium	mmol/L	None	<1.8 mmol/L >3.0 mmol/L

Chemistry			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
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
Magnesium	mmol/L	None	<1 mmol/L >4 mmol/L
Phosphorus	mmol/L	None	>0.323 mmol/L above ULN or below LLN
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

9.4. Appendix 4 – Abbreviations & Trade Marks

Abbreviations

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

IEC	Independent Ethics Committee
INR	international normal range
IP	investigational product
IRB	Institutional Review Board
ISRs	injection site reactions
ITT	intent-to-treat
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LDL-c	low density lipoproteins;
LMCF	last mean carried forward
K_2EDTA	di-potassium ethylenediaminetetraacetic acid
MACE	major adverse cardiovascular event
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MI	myocardial infarction
MSDS	Material Safety Data Sheet
MTC	medullary thyroid cancer
OC RDC	Oracle Clinical Remote Data Capture
PAC	Pancreatitis Adjudication Committee
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
PTS-DPMK	Platform Technologies and Science-Drug Metabolism and Pharmacokinetics
RAP	Reporting Analysis Plan
RBC	red blood cell
RNA	ribonucleic acid
s.c.	subcutaneous
SAC	Statistical Analysis Complete
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SRM	Study Reference Manual
SU	sulfonylureas
T2DM	type 2 diabetes mellitus
TSH	thyroid stimulating hormone
ULN	upper limit of normal range
WBC	white blood cell
WCBP	women of child bearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA

9.5. Appendix 5: List of Data Displays

9.5.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Listings	Tables
Study Population	1 to 5	1.1 to 1.5
Safety	6 to 15	1.6 to 1.7
Exploratory Endpoints	16 to 20	

9.5.2. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
[Disposition]					
1.1.	All Subjects	ES1/ES1A	Summary of Subjects Disposition for the Subject Conclusion Record		
[Demographics and Baseline Characteristics]					
1.2.	All Subjects	DM1	Summary of Demographic Characteristics		
1.3.	All Subjects	DM5	Summary of Race & Racial Combinations		
1.4.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID		
1.5.	Enrolled	DM11	Summary of Age Ranges		
Safety Tables					
1.6.	All Subjects	AE15	Summary of Common (>=2%) Non-serious AEs by System Organ Class and Preferred Term		
1.7.	All Subjects	AE16	Summary of Serious AEs by System Organ Class and Preferred Term		

9.5.3. Listings

Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.	All Subjects		Listing of Subjects with Inclusion/Exclusion Criteria Deviations		
2.	All Subjects		Listing of Reasons for Withdrawal from Study		
3.	All Subjects		Listing of Demographics and Baseline Characteristics		
4.	All Subjects		Listing of Race		
5.	All Subjects		Listing of Subjects by Site ID		
6.	All Subjects		Listing of Concomitant Medication by Generic Term		
7.	All Subjects		Listing of All Adverse Events		
8.	All Subjects		Listing of Hematology Laboratory Data		
9.	All Subjects		Listing of Chemistry Laboratory Data		
10.	All Subjects		Listing of Urinalysis Laboratory Data		
11.	All Subjects		Listing of Laboratory Data for Subjects with Any Value of Potential Clinical Concern		
12.	All Subjects		Listing of Liver Functions with Any Value of Potential Clinical Concern		
13.	All Subjects		Listing of Vital Signs		
14.	All Subjects		Listing of GCSI-DD		
15.	All Subjects		Listing of Exposure Data		
16.	Pharmacodynamic		Listing of all EGG endpoints.		
17.	Pharmacodynamic		Listing of Visual Analogue Scale (VAS) Scores (0-100mm scale)		

Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
18.	Pharmacodynamic		Listing of Gastric Emptying 13C Excreted in Breath (kPCD1) Over Time by Treatment and Visit		
19.	Pharmacodynamic		Listing of Time to Half Gastric Emptying (GET1/2) by Visit		
20.	Pharmacodynamic		Listing of Volume of Water Ingested during EGG with Water Load Test		

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

Title	:	Reporting and Analysis Plan for A Randomized, Open-label, Active-Controlled, Parallel-Group, Exploratory Study on the Effects of Repeated Doses of Albiglutide compared to Exenatide on Gastric Myoelectrical Activity and Gastric Emptying in Subjects with Type 2 Diabetes Mellitus
Compound Number	:	GSK716155
Effective Date	:	23-June-2017

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204879.
- This RAP is intended to describe the exploratory endpoints for the study Part A only.
- This study is terminated early prior to completion of Part A with a limited number of subjects (N=4) enrolled. Therefore, a synoptic CSR is planned and a brief RAP document is prepared accordingly.
- This RAP will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) Deliverable.

Author's Name and Functional Area:

PPD Principle Statistician	23-June-2017

Approved by:

PPD Dir Statistics & Programming	23-June-2017

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Purpose	To gain insight into a potential peripheral mechanism of nausea associated with glucagon-like peptide-1 receptor (GLP-1R) agonists; this study will compare the effect of albiglutide and exenatide on gastric myoelectrical activity (GMA), gastric emptying (GE) and nausea [as measured by visual analogue scale (VAS)] in subjects with type 2 diabetes mellitus (T2DM). The study is divided in two parts. Part A will characterize the GMA, GE and nausea response to exenatide and confirm exenatide as a positive control for Part B. At the time the RAP preparation, the study had terminated early with a limited number of subjects enrolled in Part A.
Protocol	• This RAP is based on the protocol amendment 1 [(Dated: 23/June/2016) of study GSK 204879 (GSK Document No. : 2015N255772_01) and eCRF Version 1.
Primary Objective	To evaluate the effect of exenatide on GMA (pilot phase).
Primary Endpoint	(All endpoints for Part A are exploratory) • Change from baseline of electrogastrogram (EGG) parameters at each recording time interval (pre-and 10, 20 and 30 min after water load) compared to baseline: o Distribution of average power by frequency region (as % of power) o Ratios of average power post- WLT/pre-WLT by frequency region o Percentage (%) of time with the dominant EGG frequencies in the four frequency ranges (bradygastria, normal, tachygastria and duodenal) • Change from baseline EGG parameters related to VAS of nausea at each recording time interval (pre-and 10, 20 and 30 min after water load) at Day 4
Study Design	• This is a single arm, open label pilot phase to evaluate the effect of 5-day repeated doses of exenatide (10 µg twice daily) on GMA, GE and nausea in subjects with T2DM. • The study will comprise 3 study periods: screening/wash-out (up to 3 weeks), treatment (5 days), and post-treatment follow-up (within 7 days after the last dose of exenatide). • The study will recruit subjects with T2DM (>6 months since diagnosis) with glycated hemoglobin (HbA1c) >6.5% and ≤9.0%, fasting plasma glucose (FPG) <=210 mg/dL (central lab) at screening and on a current regimen of diet and exercise or a stable dose of one oral anti-diabetic medication (OAM) (maintained for >= 2 months prior to screening). • Fasting capillary blood glucose will be confirmed to be <=230 mg/dL at baseline. • Subjects receiving monotherapy with an OAM of metformin, sulfonylurea, sodium glucose co-transporter-2 (SGLT2) inhibitors, or meglitinide at screening will be washed out for 2 days for immediate release and 4 days for extended release OAM prior to baseline. • Subject's nutritional plan will be optimized prior to baseline and

	maintained during the entire study. • All evaluations and assessments will be performed as outpatient visits. Subjects will undergo 2 EGG and 2 gastric emptying breath tests (GEBT) assessments. • At the end of the Part A, subjects previously on an OAM will restart OAM at the discretion of the investigator after the last dose of exenatide. The half-life of exenatide (2-3 hours) should be taken into consideration. • The total duration of a subject's participation will be approximately 5 weeks.
Planned Analyses	• **Part A**: Final Analysis: After at least 10 evaluable subjects defined as having at least one valid pre-dose EGG and one valid post –dose EGG, the final analysis for the clinical study report will be performed. At this time, the database will be frozen. The study is terminated early with a limited number of subjects enrolled in Part A.
Analysis Populations	The analysis set will include subjects who have taken at least one dose of study medication and one valid EGG data. Data will be assessed and reviewed by the central reader before it is considered valid.
Hypothesis	No formal statistical hypotheses are being tested in Part A. Part A will be a pilot phase investigating the effect of repeated doses of exenatide on GMA, GE, and VAS of nausea.
Primary Analyses	No formal statistical analyses will be performed for the exploratory endpoints for Part A. All exploratory endpoints will be assessed using descriptive statistics and graphical displays as appropriate.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

The study terminated early with a limited number of subjects enrolled in Part A. Therefore, only data listings will be produced for selected data. These are limited in scope compared to the originally planned statistical analysis specified in the protocol amendment 1 [(Dated: June 23, 2016)].

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

Part A:

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the effect of exenatide on GMA	• Change from baseline of EGG parameters at each recording time interval (pre-and 10, 20 and 30 min after water load) compared to baseline: o Distribution of average power by frequency region (as % of power) o Ratios of average power post- WLT/pre-WLT by frequency region o Percentage (%) of time with the dominant EGG frequencies in the four frequency ranges (bradygastria, normal, tachygastria and duodenal) • Change from baseline EGG parameters related to VAS of nausea at each recording time interval (pre-and 10, 20 and 30 min after water load) at Day 4
To assess the effect of exenatide on GE	• Change from baseline of time to half gastric emptying (GEt½) at Day 5 • Change from baseline of profiles of 13C excreted in breath (kPCD1) at Day 5 and at each time interval (45, 90, 120, 150, 180 and 240 min).
To assess the volume of water ingested during EGG	Change from baseline of volume of water ingested during EGG with water load test at Day 4.
To evaluate the effect of exenatide on stomach fullness, hunger, bloating and abdominal pain during EGG with water load test	Change from baseline of VAS of stomach fullness, hunger, bloating and abdominal pain during the EGG water load test at each time interval (pre-and 10, 20 and 30 min after water load) at Day 4
To evaluate safety and tolerability of exenatide	• Vital signs, clinical laboratory tests, AEs, and GCSI-DD. • Nausea AEs presenting outside the timing of the WLT and GCSI-DD.

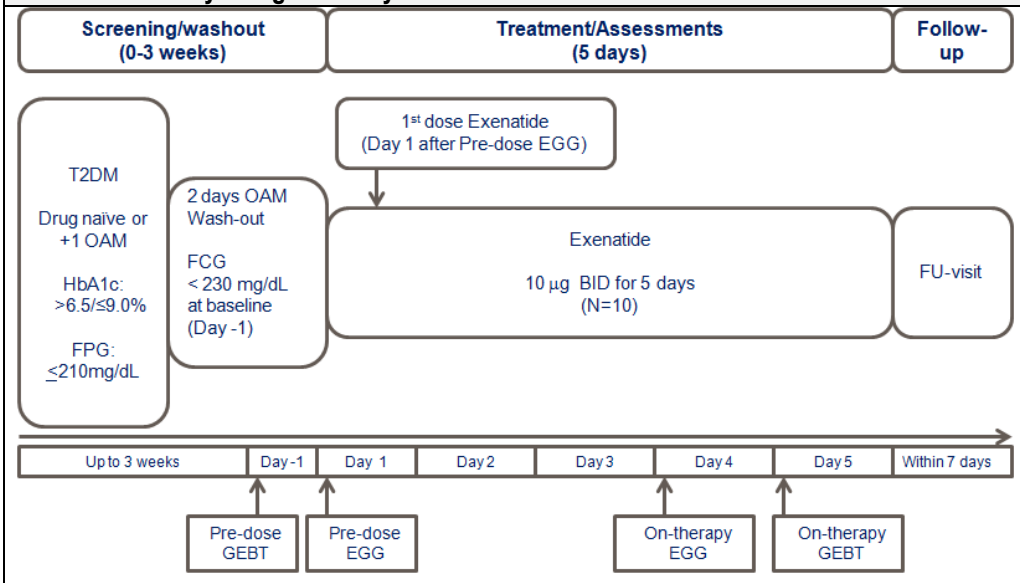
Objectives	Endpoints
To evaluate change in gastric rhythm status (Data permitting)	At Day 4; over 30 min and at each time interval (pre-and 10, 20 and 30 min after • water load). • Number and % of subjects with a shift in gastric rhythm status. • Number and % of subjects by gastric rhythm status at each time interval. • Mean and mean change from baseline in • average dominant frequency

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

2.3. Study Design

2.3.1. Overview of Study Design and Key Features

Overview of Study Design and Key Features Part A



Design Features	Part A is a single arm, open label pilot phase 5-days of treatment.
Dosing	All subjects will receive 10 µg subcutaneous exenatide twice daily for 5 days. The total duration of a subject's participation will be approximately 5 weeks.
Interim Analysis	No interim analysis is planned for this study.

Due to early termination, the entirety of the study conduct was not carried out.

2.3.2. Study Design

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

At the time the RAP is being prepared, the study is terminated early with a limited number of subjects enrolled in Part A.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned for this study.**Final Analyses**

The final planned primary analyses will be performed after the completion of the following sequential step:

All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Part A: Pharmacodynamic	Comprise of all subjects who have taken at least one dose of study medication and one valid EGG data Data will be assessed and reviewed by the central reader before it is considered valid. The central reader will provide the valid data that will be used for the analyses.	Pharmacodynamic
All Subjects	All subjects with at least one dose of study medication.	Safety
Enrolled	All enrolled subjects.	Enrolled

NOTES :

- Please refer to Appendix 5: List of Data Displays which details the population to be used for each displays being generated.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Reporting Conventions

- All data displays will be presented according to the Integrated Data Standards Library (IDSL) reporting standards, where applicable.
- Analyses will be performed using the 9.1.3 version of the SAS System or higher (SAS is a registered trademark of the SAS Institute Inc., Cary, NC, USA). Programs will be imported into HARP and the final output will be produced by running drivers in HARP.
- Data collected at unplanned (i.e. unscheduled) time points will not be included in the summaries by visit unless otherwise stated. Unscheduled or unplanned readings will be presented in the listings and they will be included when determining worst-case flagging for post-baseline summaries.
- In all data displays, planned and actual relative times will be relative to the study drug dosing time of the relevant dosing session.

- Refer to IDSL standards (when applicable) for decimal place conventions. Raw data will generally be presented to the same number of decimal places as it was collected.
- All data will be reported according to the actual treatment the subject received. Any departures from the planned treatment according to the randomization schedule will be documented in the report.
- All observations that occurred prior to dosing will be considered as part of the pre-dose period. All observations that occur during dosing will be attributed to the subject's treatment.

Deviations from the analyses in the RAP will be identified in the final clinical study report.

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
9.1	Appendix 1: Time & Events
9.2	Appendix 2: Assessment Windows
9.3	Appendix 3: Values of Potential Clinical Importance
9.4	Appendix 4: Abbreviations and Trademarks
9.5	Appendix 5: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 5: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated		
	Figure	Table	Listing
Subject Disposition			
Reasons for Withdrawal from Study		Y	Y
Demography and Baseline Characteristics			
Demographics and Baseline Characteristics		Y	Y
Race & Racial Combinations		Y	Y
Number of subjects by Site ID		Y	Y
Age Ranges		Y	
Medical Condition & Concomitant Medications			
Concomitant Medication			Y
Exposure			
Exposure to Study Drug			Y

Note: additional tables, listings and figures will be provided in Appendix 5: List of Data Displays.

- Y = Yes display generated.

Following review of the data, additional analyses maybe conducted to further support the evaluation and interpretation of the data.

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, 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, if appropriate.

6.3. Exposure to Study Drug

A by-subject listing of study drug administration will also be presented. Overall study drug administration and treatment compliance will be present with the exposure to study drug listing.

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.

6.5. Safety Analyses

6.5.1. Overview of Planned Analyses

The safety analyses will be based on all subjects population.
Table 3 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 5: List of Data Displays.

Table 3 Overview of Planned Safety Analyses

Endpoints	Observed				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Adverse Events	**Y**			Y				
Clinical Laboratory				Y				
Vital Signs				Y				
GCSI-DD				Y				

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

Following review of the data, additional analyses maybe conducted to further support the evaluation and interpretation of the data.

6.5.2. Adverse Events

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

All AEs will be listed in a subject data listing.

6.5.3. Clinical Laboratory Evaluations

6.5.3.1. Chemistry, Hematology and Urinalysis

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 central lab for the study records.

Hematology parameters include red blood count, hemoglobin, hematocrit white blood cell count with differential, and platelet count. Chemistry blood urea nitrogen (BUN), potassium, aspartate aminotransferase (AST), total and direct bilirubin, creatinine, sodium, ALT, total protein, calcium, magnesium, chloride, phosphorus albumin, , gamma glutamyl transferase (GGT), estimated glomerular filtration rate (eGFR), and lipids

(including total cholesterol, LDL-C, HDL C, triglycerides,). Urinalysis parameters include microalbumin and creatnine and specific gravity, pH, glucose, nitrates, leukocytes esterase, blood and ketones by dipstick and microscopic examination (if blood or protein is abnormal).

All laboratory parameters as collected will be presented in by-subject listings at every scheduled assessment time point. All listings will be done for the safety population and all laboratory data will be listed including other laboratory tests, such as TSH, and urine pregnancy test results.

Additionally, the number of subjects with laboratory values of potential clinical concern will be provided in a listing by treatment group and scheduled assessment time point for hematology and chemistry. The criteria for laboratory values of potential clinical concern are detailed in Appendix 3: Values of Potential Clinical Importance.

A listing of laboratory values of potential clinical concern will be provided for liver function tests, including ALT, AST, and total bilirubin. The criteria for liver function tests of potential clinical concern are detailed in Appendix 3: Values of Potential Clinical Importance.

6.5.4. Vital Signs

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

Each vital sign parameter at every scheduled assessment time point will be presented in by-subject listings. .

All listings will be produced for all subjects population.

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

The GCSI-DD consists of nine symptom severity items covering the following domains: nausea/vomiting; fullness/early satiety, and bloating. In addition, the GCSI-DD contains two symptom severity items upper abdominal pain and overall rating of gastroparesis symptoms. Patients rate each symptom on a 6-point scale from 0 – 5 with lower scores representing less symptom severity. All questions addressed in the GCSI-DD and the overall severity question will be listed in a subject data listing and by time point.

7. OTHER STATISTICAL ANALYSES (EXPLORATORY)

7.1. Overview of Planned Analyses

The study was terminated early and therefore no analysis will be performed but data listing will be generated for all exploratory endpoint as in Appendix 5.

7.2. Exploratory Analyses

Listing will be provided for all endpoints.

8. REFERENCES

None.

9. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 9.1	Appendix 1: Time and Events
Section 9.2	Appendix 2: Assessment Windows
Section 9.3	Appendix 3: Values of Potential Clinical Importance
Section 9.4	Appendix 4: Abbreviations & Trade Marks
Section 9.5	Appendix 5: List of Data Displays

9.1. Appendix 1 Time & Events

9.1.1. Protocol Defined Time & Events Part A

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

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

1. **Before baseline assessment (Day -1)**, the investigator must review **all** inclusion and exclusion criteria to confirm subject's eligibility. If a subject no longer meets all of the eligibility criteria, **do not administer the study treatment** and contact the Medical Monitor to discuss how to proceed (e.g., to determine if repeat testing is warranted).
2. For subjects taking OAM at screening only. At a minimum, two day washout for immediate release and at minimum 4 day washout for extended release OAMs. See footnote 13. For information on restarting OAM refer to Section 6.9.
3. A small meal will be provided 2 hrs prior to the EGG procedure (Section 7.3.1). A meal will also be provided post-procedure for both the EGG and GEBT.
4. Details of full and brief physical examinations are provided in Section 7.4.3.
5. SAEs related to study participation only.
6. The GCSI-DD questionnaire will be completed after the standard AE questions have been answered.
7. Clinical chemistry, hematology, urinalysis and lipid assessments are described in Section 7.4.6. Lipids will be assessed at screening only.
8. Fasting capillary glucose will be measured prior to administration of exenatide. On GEBT (Day 5) or EGG (Day 1 and Day 4) assessment days, fasting capillary glucose will be measured prior to the GEBT or EGG procedure.
9. Subjects will be provided with diet and exercise guidance (see Section 7.4.8) and instructed on self monitoring blood glucose at screening (See Section 7.4.9). Subject will be instructed to bring in their glucometers at each visit for review. Diet/exercise/SMBG reinforced at subsequent visits.
10. Informed consent for optional genetic research should be obtained before collecting a sample.
11. On the morning of Day 1, subjects will receive instructions and training on exenatide self administration and will be monitored by medical staff at the clinic during administration of the first dose. The first dose of exenatide will be administered after the baseline EGG procedure and before the post-procedure meal.
12. On Day 4 and 5, the morning dose of exenatide will be administered at clinic 1 hr (±15 min) before the EGG or GEBT procedure.
13. Every effort should be made to schedule the procedures on the nominal visit day identified. However, in order to meet scheduling needs, subjects taking OAM can schedule Day-1 up to 3 days prior to Day 1 and the OAM stopped at least the day before the GEBT . For subjects treated with diet and exercise alone Day-1 can occur within 7 days prior to Day 1. The EGG and GEBT should not be scheduled on the same day

Note: section noted in time and event table referring to the protocol.

9.2. Appendix 2 Assessment Windows

9.2.1. 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).

9.3. Appendix 3 Values of Potential Clinical Importance

9.3.1. 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 Nitrogen	mmol/L	None	>2 x ULN
Calcitonin	pmol/L	None	>100
Calcium	mmol/L	None	<1.8 mmol/L >3.0 mmol/L

Chemistry			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
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
Magnesium	mmol/L	None	<1 mmol/L >4 mmol/L
Phosphorus	mmol/L	None	>0.323 mmol/L above ULN or below LLN
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

9.4. Appendix 4 – Abbreviations & Trade Marks

Abbreviations

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

IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	international normal range
IP	investigational product
IRB	Institutional Review Board
ISRs	injection site reactions
ITT	intent-to-treat
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LDL-c	low density lipoproteins;
LMCF	last mean carried forward
K_2EDTA	di-potassium ethylenediaminetetraacetic acid
MACE	major adverse cardiovascular event
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MI	myocardial infarction
MSDS	Material Safety Data Sheet
MTC	medullary thyroid cancer
OC RDC	Oracle Clinical Remote Data Capture
PAC	Pancreatitis Adjudication Committee
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
PTS-DPMK	Platform Technologies and Science-Drug Metabolism and Pharmacokinetics
RAP	Reporting Analysis Plan
RBC	red blood cell
RNA	ribonucleic acid
s.c.	subcutaneous
SAC	Statistical Analysis Complete
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SRM	Study Reference Manual
SU	sulfonylureas
T2DM	type 2 diabetes mellitus
TSH	thyroid stimulating hormone
ULN	upper limit of normal range
WBC	white blood cell
WCBP	women of child bearing potential

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9.5. Appendix 5 List of Data Displays

9.5.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Listings	Tables
Study Population	1 to 5	1.1 to 1.5
Safety	6 to 14	1.6 to 1.7
Exploratory Endpoints	15	

9.5.2. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
[Disposition]					
1.1.	All Subjects	ES1/ES 1A	Summary of Subjects Disposition for the Subject Conclusion Record		
[Demographics and Baseline Characteristics]					
1.2.	All Subjects	DM1	Summary of Demographic Characteristics		
1.3.	All Subjects	DM5	Summary of Race & Racial Combinations		
1.4.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID		
1.5.	Enrolled	DM11	Summary of Age Ranges		
Safety Tables					
1.6.	All Subjects	AE15	Summary of Common (>=2%) Non-serious AEs by System Organ Class and Preferred Term		
1.7.	All Subjects	AE16	Summary of Serious AEs by System Organ Class and Preferred Term		

9.5.3. Listings

Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.	All Subjects		Listing of Subjects with Inclusion/Exclusion Criteria Deviations		
2.	All Subjects		Listing of Reasons for Withdrawal from Study		
3.	All Subjects		Listing of Demographics and Baseline Characteristics		
4.	All Subjects		Listing of Race		
5.	All Subjects		Listing of Subjects by Site ID		
6.	All Subjects		Listing of Concomitant Medication by Generic Term		
7.	All Subjects		Listing of All Adverse Events		
8.	All Subjects		Listing of Hematology Laboratory Data		
9.	All Subjects		Listing of Chemistry Laboratory Data		
10.	All Subjects		Listing of Urinalysis Laboratory Data		
11.	All Subjects		Listing of Laboratory Data for Subjects with Any Value of Potential Clinical Concern		
12.	All Subjects		Listing of Liver Functions with Any Value of Potential Clinical Concern		
13.	All Subjects		Listing of Vital Signs		
14.	All Subjects		Listing of GCSI-DD		
15.	Pharmacodynamic		Listing of all EGG endpoints.		