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

Title	:	Reporting and Analysis Plan for An open-label extension to Study 200952 in Subjects with Type 2 Diabetes Mellitus to Assess the Long-term Safety and Tolerability of Albiglutide Liquid Drug Product
Compound Number	:	GSK716155
Effective Date	:	06-MAR-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 204682.
- This RAP is intended to describe the safety analyses required for the study.
- The study is terminated early with a limited number of subjects (N=8) enrolled and limited data collected (only available at Early Withdrawal and Follow-up visits except one subject had Week 30 visit). 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 content of the final Statistical Analysis Complete (SAC) Deliverable.

Author's Name and Functional Area:

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Senior Biostatistician, PPD	Biostatistics Team Lead, PPD	

Approved by:

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• This study will evaluate the long-term safety, tolerability and pharmacodynamics of albiglutide liquid drug product in subjects with type 2 diabetes mellitus (T2DM) who have completed Study 200952 and satisfy all inclusion/exclusion criteria to enter Study 204682.
Protocol	• This RAP is based on the protocol (Dated: 28/OCT/2015) of study GSK204682 (GlaxoSmithKline Document Number. : 2015N235104_00] and eCRF Version 2.
Primary Objective	• To evaluate extended safety, tolerability and immunogenicity data of albiglutide liquid product.
Primary Endpoint	• AEs and SAEs, clinical laboratory evaluations, physical examinations, vital signs and ECGs • Anti-albiglutide antibody production over time
Study Design	• This is a 26 week, open-label, single group, multicenter, extension study to Study 200952. This extension study will provide extended safety, tolerability and immunogenicity for the albiglutide liquid drug product. • The extension study will recruit subjects who have completed Study 200952 and satisfy all inclusion/exclusion criteria. Subjects will continue on their current regimen of diet and exercise or stable dose of background metformin (if applicable). • This extension study will comprise 2 study periods: treatment (26 weeks) and post-treatment follow-up (8 weeks). • While at the time the RAP is being prepared, the study is terminated early with a limited number of subjects enrolled. • All subjects will receive 50 mg albiglutide liquid drug product via auto-injector.
Analysis Populations	• Safety Population

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

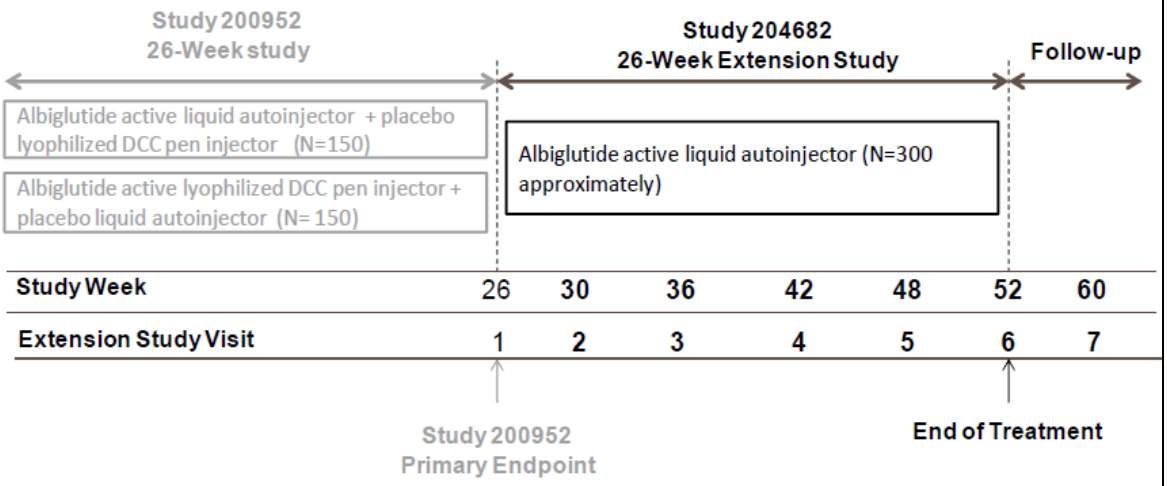
The statistical analysis plan will be done on a limited number of subjects and data (not the full 26 weeks as planned) due to early termination. Only summary for demography and listings for key safety data and immunogenicity will be provided.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate extended safety, tolerability and immunogenicity data of albiglutide liquid product.	• AEs and SAEs, clinical laboratory evaluations, physical examinations, vital signs and ECGs • Anti-albiglutide antibody production over time

2.3. Study Design

2.3.1. Overview of Study Design and Key Features

Overview of Study Design and Key Features	
	
Design Features	• Open-label, single group, multicenter, extension study to Study 200952
Dosing	• Subjects will receive 50 mg albiglutide liquid drug product via auto-injector for 26 weeks.. • Study treatment will be administered once weekly by subcutaneous (s.c.) injection in the abdomen, thigh, or upper arm. • The first dose of study treatment will be administered by the subject during the clinic visit (Visit 1, week 26) with supervision from clinic staff. All further doses of study treatment will be self-administered by the subject.
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

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

This study will comprise 2 study periods: treatment (26 weeks) and post-treatment follow-up period (8 weeks).

The extension study will recruit subjects who have completed Study 200952 and satisfy all inclusion/exclusion criteria. Subjects will continue on their current regimen of diet and exercise or stable dose of background metformin (if applicable).

Study treatment will be administered once weekly by s.c. injection in the abdomen, thigh, or upper arm. Subjects will receive 50 mg albiglutide liquid drug product via auto-injector for 26 weeks. The first dose of study treatment will be administered by the subject during the clinic visit (Visit 1, week 26) with supervision from clinic staff. All further doses of study treatment will be self-administered by the subject.

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

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 step:

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Safety	• Comprise of all enrolled subjects who receive at least one dose of study treatment. • This population will be analysed according to the treatment the subject actually received.	• Safety

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

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
Section 10.1	Appendix 1: Time & Events
Section 10.2	Appendix 2: Assessment Windows
Section 10.3	Appendix 3: Values of Potential Clinical Importance
Section 10.4	Appendix 4: Abbreviations and Trademarks
Section 10.5	Appendix 5: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

Table 2 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
Demography and Baseline Characteristics			
Demographics and Baseline Characteristics		Y	Y
Race & Racial Combinations			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

Demographic and baseline characteristics will be based on the data from the main study 200952 as this is an extension study.

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 and ethnicity 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 and based on the data from the main study 200952.

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 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. SAFETY AND TOLERABILITY ANALYSES

7.1. Overview of Planned Analyses

The safety analyses will be based on the safety 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				
Clinical Laboratory				Y				
Vital Signs				Y				
Electrocardiogram (ECG)				Y				
Immunogenicity				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.

7.2. 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.

7.3. Clinical Laboratory Evaluations

7.3.1. 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 complete blood count with red blood cell indices, white blood cell count with differential, and platelet count. Chemistry parameters (including lipids) include blood urea nitrogen (BUN), potassium, aspartate aminotransferase (AST), total and direct bilirubin, creatinine, sodium, ALT, total protein, calcium, chloride, alkaline phosphatase (ALP), albumin, bicarbonate, uric acid, gamma glutamyl transferase (GGT), estimated glomerular filtration rate (eGFR), and lipids (including total cholesterol, LDL-C, HDL C, triglycerides, free fatty acids). Urinalysis parameters include specific gravity, pH, glucose, protein, 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 from Study 200682 and also Week 26 from Study 200952. All listings will be done for the safety population and all laboratory data will be listed including other laboratory tests, such as HIV, Lipase, Amylase, hepatitis B, hepatitis C, 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.

7.4. 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 the safety population.

7.5. Electrocardiograms

ECG parameters collected at each scheduled assessment time point include heart rate, QRS interval, QT interval, QT interval – Bazett correction (QTcB) (if applicable), QT interval – Fridericia correction (QTcF), RR interval and PR interval.

Each ECG parameter at each scheduled assessment time point will be presented in by-subject listings. All listings will be produced for the safety population.

7.6. Immunogenicity

The immunogenicity data will be listed. Immunogenicity listings will be generated only after the unblinding of Study 200952.

8. OTHER STATISTICAL ANALYSES

Not applicable.

9. REFERENCES

GlaxoSmithKline Document Number 2015N235104_00. Protocol 204682: An Open-label Extension to Study 200952 to Evaluate the Long-term Safety, Tolerability and Pharmacodynamics of Albiglutide Liquid Drug Product in Subjects with Type 2 Diabetes Mellitus (28-OCT-2015)

10. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.1	Appendix 1: Time & Events
Section 10.2	Appendix 2: Assessment Windows
Section 10.3	Appendix 3: Values of Potential Clinical Importance
Section 10.4	Appendix 4: Abbreviations and Trademarks
Section 10.5	Appendix 5: List of Data Displays

10.1. Appendix 1: Time & Events

10.1.1. Protocol Defined Time & Events

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

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

1. **Before dosing**, the investigator must review **all** inclusion and exclusion criteria to confirm subject's eligibility. If a subject no longer meets all of the eligibility criteria (e.g., there is evidence of a new myocardial infarction (MI) on an ECG or ALT, etc. are out of range), **do not administer the study treatment** and contact the medical monitor to discuss how to proceed (e.g., to determine if repeat testing is warranted).
2. Details of full and brief physical examinations are provided in Protocol Section 7.3.3.
3. 12-lead ECGs will be obtained **before** measurement of vital signs and collection of blood samples for laboratory testing. See Protocol Section 7.3.5.
4. Clinical chemistry and hematology assessments are described in Protocol Section 7.3.6.
5. Urine samples should be collected in the early morning.
6. Blood samples for HbA_{1c} should be collected before administration of study treatment.
7. Subjects will have their FPG and HbA_{1c} levels evaluated to monitor for potential hyperglycemia.

8. Blood samples for immunogenicity are to be collected **before** study drug administration.
9. Standard diabetic dietary and exercise advice will be reinforced through the end-of-treatment visit.
10. Compliance will be assessed as described in Protocol Section 6.7.
11. Subjects who discontinue study treatment should be handled as described in Protocol Section 5.4.
12. Follow-up visit for subjects who have discontinued study treatment (see Protocol Section 5.4), or subjects who have completed the 52 week treatment period.
13. Visit 1of 204682 is also the end of treatment visit in Study 200952.
14. Visit 1 of Study 204682; albiglutide liquid drug product administered to all study subjects.

10.2. Appendix 2: Assessment Windows

10.2.1. 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 dose of assessment >= first dose date
- Study day = date of assessment – date of first dose, if dose 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).

10.2.2. Visit Slotting Algorithm

For all safety parameters to be summarized by visit, nominal visits recorded on the eCRF will be used for the summaries. No visit slotting algorithm will be applied.

10.3. Appendix 3: Values of Potential Clinical Importance

10.3.1. 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

Chemistry			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
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
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

10.4. 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
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

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NONE

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MedDRA

10.5. Appendix 5: List of Data Displays

10.5.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Listings	Tables
Study Population	1 to 4	1
Safety	5 to 17	

10.5.2. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
[Demographics and Baseline Characteristics]					
1.1.	[Safety]		Demographic Characteristics		

10.5.3. Listings

Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.	[Safety]		Inclusion/Exclusion Criteria Deviations		
2.	[Safety]		Demographics and Baseline Characteristics		
3.	[Safety]		Geographic Ancestry		
4.	[Safety]		Concomitant Medications		
5.	[Safety]		Albiglutide Administration		
6.	[Safety]		Adverse Events		
7.	[Safety]		Hematology Laboratory Evaluations		
8.	[Safety]		Chemistry Laboratory Evaluations		
9.	[Safety]		Urinalysis Laboratory Evaluations		
10.	[Safety]		Laboratory Data for Subjects with Any Value of Potential Clinical Importance		
11.	[Safety]		Liver Functions with Any Value of Potential Clinical Importance		
12.	[Safety]		Vital Signs		
13.	[Safety]		ECG Values		
14.	[Safety]		Overall ECG Interpretations		
15.	[Safety]		Product Investigator's Comments		
16.	[Safety]		Drug Accountability		
17.	[Safety]		Immunogenicity Information: Anti-Albiglutide Antibody		