

TITLE PAGE

Division: Worldwide Development

Information Type: Protocol Amendment

Title:	Study 200977: Albiglutide + Insulin Glargine Versus Insulin Lispro + Insulin Glargine in the Treatment of Subjects With Type 2 Diabetes Mellitus: The Switch Study
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PPD

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2013N187697_01	2014-AUG-14	Republished
Republished to update the PGx sections with the new 'genetics' language from new protocol template		
2013N187697_02	2015-JUN-01	Amendment No. 1
<p>Changes reflected in Protocol Amendment No. 1 have been included to address the following:</p> <ul style="list-style-type: none"> • Clarify potentially confusing text • Add details of sensitivity analyses that will assess the impact of missing data for the noninferiority test • Introduce additional flexibility into glycemic eligibility criteria at Screening and to the process for transitioning subjects from their prior basal-bolus insulin therapy to insulin glargine and insulin lispro at the beginning of the Standardization Period, as well as provide additional flexibility to the investigator when adjusting insulin glargine and insulin lispro • Further mitigate the potential risk of hypoglycemia, as well as enhance subject education and training pertaining to hypoglycemic events • Add an optional fasting HbA_{1c} test at Screening to aid investigators in the selection of subjects who may be good candidates for the study • Add a stimulated C-peptide assessment at Screening as a complimentary assessment for subjects to demonstrate reserve insulin secretory capacity • Incorporate other administrative changes 		
2013N187697_03	2015-JUN-10	Amendment No. 2, Country-Specific Protocol Amendment for Applicable Sites in Germany Only
<ul style="list-style-type: none"> • The inclusion criterion pertaining to adequate contraception was updated to indicate that progestogen-only pills are only acceptable if they have a Pearl Index of less than 1.0. • A criterion was added to exclude persons who have been put in an institution because of official or legal order. • A criterion was added to exclude employees (or the employee's relatives) of the sponsor, the contract research organization, or the investigative site. 		

2013N187697_04	2015-SEP-24	Amendment No. 3
<p>Changes reflected in Protocol Amendment No. 3 have been included to address the following:</p> <ul style="list-style-type: none">• Correct SI units for select blood glucose concentrations (mmol/L) for insulin titration• Combine global amendment 01 and country-specific amendments into a single protocol document. To aid clarity, country-specific requirements have been clearly identified• Incorporate other administrative changes		

SPONSOR SIGNATORY

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PPD is the contract research organization for this study.

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200977

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

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

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

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

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANSM	Agence nationale de sécurité du médicament et des produits de santé
AST	aspartate aminotransferase
β-HCG	β-human chorionic gonadotropin
CNIL	Commission nationale de l'informatique et des Libertés
CRA	clinical research assistant
CTR	clinical trial registry
CV	cardiovascular
dL	deciliter
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FA	full analysis
FDA	Food and Drug Administration
FPG	fasting plasma glucose
g	gram
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
GSK	GlaxoSmithKline
HbA _{1c}	glycosylated hemoglobin
HFS-II	hypoglycemia fear survey-II
IB	investigator's brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IT	information technology
IU	international unit
IVRS	interactive voice response system
kg	kilogram
L	liter
LMCF	last mean carried forward
m	meter
MAR	missing at random
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction

min	minute
mL	milliliter
mmol	millimole
MMRM	mixed-effect model with repeated measures
MNAR	missing not at random
OAD	oral antidiabetic
OC RDC	Oracle Clinical Remote Data Capture System
PAC	pancreatitis adjudication committee
PK	pharmacokinetic
PP	per protocol
RAP	reporting and analysis plan
SAE	serious adverse event
SMBG	self-monitored blood glucose
SPM	Study Procedures Manual
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
TRIM-Diabetes	treatment-related impact measure for diabetes
TSH	thyroid-stimulating hormone
ULN	upper limit of normal

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PROTOCOL SUMMARY

Rationale

The therapeutic aim of mealtime insulin is to blunt postprandial glycemic excursions, which can be extreme in some individuals, resulting in poor control during the day [Inzucchi, 2012]. Well-managed basal-bolus therapy provides a flexible way of controlling glucose throughout the day and night since dosing can be timed to approximate nondiabetic endogenous insulin release. However, in practice, basal-bolus insulin therapy is quite challenging to manage well for both physicians and patients. Moreover, declining health and cognition tend to exacerbate the insulin management challenge in many older type 2 diabetes mellitus (T2DM) patients. In comparison to endogenous insulin, basal-bolus insulin therapy comes with a plethora of issues [Swinnen, 2009; McCoy, 2012; Hessler, 2014], such as

- Dose-dependent increased risk of hypoglycemia
- Dose-dependent increased mortality risk associated with hypoglycemia;
- Increased risk of weight gain
- Encumbered quality of life associated with need to balance insulin dosing and carbohydrate intake, in both timing and magnitude
- Cost and stress of multiple daily injections
- Earlier loss of independence with aging due to the complexities of diabetes management with insulin

Treatments that diminish insulin demand and preserve or enhance β -cell function are expected to result in better glycemic control and diminished risk of these insulin therapy complications.

Combining a marketed glucagon-like peptide-1 receptor (GLP-1R) agonist with basal insulin is part of the current treatment armamentarium for T2DM; however, none of these agents are currently indicated for use in product labeling with bolus insulin. Two studies have reported reductions in prandial insulin doses following the addition of exenatide with no major hypoglycemic events [Yoon, 2009; Viswanathan, 2007]. Liraglutide, when used in combination with a basal-bolus insulin regimen in patients with T2DM, allowed for a reduction in total and bolus insulin doses [Lane, 2014]. However, the Association of British Clinical Diabetologists' audit revealed a worsening of glycemic control for almost 50% of patients who stopped insulin therapy upon initiation of exenatide; thus, it is recommended that insulin be reduced but not discontinued once a significant glycemic improvement has been observed after initiating therapy with a GLP-1R agonist [Thong, 2011]. The difficulty of how fast and how far to downtitrate insulin doses without compromising glycemic control has been recognized in reviews of GLP-1R agonists [Holst, 2013] and is still an open question.

The Phase IIIa clinical development program for albiglutide included 2 studies with insulin, both open-label, the first comparing albiglutide with insulin glargine (Study GLP112754) and the second comparing albiglutide when added on to insulin

glargine versus insulin lispro added on to insulin glargine (Study GLP108486). At their respective primary endpoints (Week 52 in Study GLP112754 and Week 26 in Study GLP108486), both studies showed that albiglutide was statistically noninferior to each insulin treatment approach with regard to HbA_{1c} and demonstrated that albiglutide could be used as an alternative to insulin therapy in patients with late-stage T2DM. Despite comparable glucose lowering, albiglutide therapy was associated with approximately 1.5- to 2-fold less symptomatic hypoglycemia and with weight loss rather than weight gain compared with the addition of insulin (treatment difference of 1.5 to 2.6 kg).

This study will evaluate the efficacy and safety of once-weekly albiglutide administered in combination with basal insulin as a replacement for bolus insulin in subjects with T2DM who are currently managed with a basal-bolus insulin regimen but who are not achieving glycemic treatment goals. It is expected that subjects switched to albiglutide plus basal insulin (with discontinuation of bolus insulin therapy) compared with those intensifying basal-bolus insulin therapy will be able to maintain glycemic control with less hypoglycemia and less weight gain, while also demonstrating a reduced total daily insulin requirement and reduced number of weekly injections (e.g., 28 injections per week [7 basal insulin and up to 21 bolus insulin injections] in basal-bolus-treated subjects compared with potentially 8 injections per week [1 weekly albiglutide injection and 7 basal injections] in subjects switching to basal insulin plus albiglutide).

Data from this study will support the concept that albiglutide is a potential alternative to bolus insulin that will simplify insulin therapy in subjects with T2DM that do not reach adequate control with basal-bolus therapy.

Objectives and Endpoints

Objective	Endpoint
Primary	
<ul style="list-style-type: none"> To evaluate the glycemic effectiveness of once-weekly albiglutide as replacement of prandial insulin in subjects with T2DM receiving basal-bolus insulin therapy 	<ul style="list-style-type: none"> Change from Baseline in HbA_{1c} at Week 26
Secondary	
<i>Key Secondary</i>	
<ul style="list-style-type: none"> To determine the proportion of subjects treated with once-weekly albiglutide that are able to replace prandial insulin without the need for re-introduction of insulin lispro 	<ul style="list-style-type: none"> Proportion of subjects treated with once-weekly albiglutide that are able to discontinue insulin lispro at Week 4 and do not meet prespecified criteria for severe, persistent hyperglycemia through Week 26
<ul style="list-style-type: none"> To demonstrate a significant difference in the frequency of hypoglycemic events between treatment groups 	<ul style="list-style-type: none"> Percentage of subjects with severe or documented symptomatic hypoglycemia through Week 26 (see Section 6.3.1)
<ul style="list-style-type: none"> To demonstrate a significant difference in body weight between treatment groups 	<ul style="list-style-type: none"> Change from Baseline in body weight at Week 26 and over time

Objective	Endpoint
<ul style="list-style-type: none"> To demonstrate a significant reduction in total daily dose of insulin between treatment groups 	<ul style="list-style-type: none"> Total daily insulin dose at Week 26
<i>Supportive Secondary</i>	
<ul style="list-style-type: none"> To assess additional glycemic parameters, achievement of HbA_{1c} treatment goals, body weight, and total daily insulin dose 	<ul style="list-style-type: none"> Additional glycemic parameters: <ul style="list-style-type: none"> HbA_{1c} change from Baseline over time Fasting plasma glucose (FPG) change from Baseline at Week 26 and over time Achievement of HbA_{1c} treatment goals: <ul style="list-style-type: none"> Proportion of subjects achieving a HbA_{1c} <7.0% at Week 26 and over time Proportion of subjects achieving a HbA_{1c} <6.5% at Week 26 and over time Incidence and time to meeting prespecified criteria for severe, persistent hyperglycemia at Week 26 Additional assessments of daily insulin doses: <ul style="list-style-type: none"> Total daily insulin dose (24-hour total international units [IU] and total units/kg body weight) over the 3 days preceding the Baseline/Randomization and Week 4, 10, and 18 visits Total daily basal insulin (insulin glargine) (24-hour total IU and total units/kg body weight) over the 3 days preceding the Baseline/Randomization and Week 4, 10, 18, and 26 visits Total daily bolus insulin (insulin lispro) (24-hour total IU and total units/kg body weight) over the 3 days preceding the Baseline/Randomization and Week 4, 10, 18, and 26 visits Total number of weekly insulin injections (7 days) to achieve glycemic control at Baseline/Randomization and Week 4, 10, 18, and 26 Composite endpoints (after 26 weeks of treatment): <ul style="list-style-type: none"> Percentage of subjects achieving HbA_{1c} <7.0% without weight gain Percentage of subjects achieving HbA_{1c} <7.0% without severe or documented symptomatic hypoglycemia

Objective	Endpoint
	<ul style="list-style-type: none"> Percentage of subjects achieving HbA_{1c} <7.0% without weight gain and without severe or documented hypoglycemia
<ul style="list-style-type: none"> To evaluate the safety and tolerability of the 2 treatment groups 	<ul style="list-style-type: none"> Adverse events (AEs) and serious AEs (SAEs), including AEs and SAEs leading to discontinuation of randomized study medication Other AEs of special interest (for example, cardiovascular [CV] events, gastrointestinal [GI] events, injection site reactions, potential systemic allergic reactions, pancreatitis, pancreatic cancer, medullary thyroid cancer, malignant neoplasms following treatment with insulin, diabetic retinopathy events, appendicitis, liver events, pneumonia, and atrial fibrillation/flutter) Assessments of hypoglycemia: <ul style="list-style-type: none"> Percentage and number of events of hypoglycemia with confirmed home blood glucose monitoring and/or third-party intervention through Week 26 (i.e., severe, documented symptomatic, and asymptomatic hypoglycemic events, see Section 6.3.1) in 3-month intervals (i.e., from Baseline/Randomization to Week 12, >Week 12 to Week 26) Incidence of hypoglycemic events (in total and by each category as defined by the American Diabetes Association criteria) Incidence of daytime hypoglycemia (in total and by category), defined as hypoglycemic events with an onset between 06:00 hours and 00:00 hours (inclusive), and nocturnal hypoglycemia (in total and by category), defined as hypoglycemic events with an onset between 00:01 hours and 05:59 hours (inclusive) Incidence of hypoglycemia with blood glucose <56 mg/dL (<3.1 mmol/L), regardless of symptoms Assessment of clinical laboratory tests (hematology, clinical chemistry, urinalysis,

Objective	Endpoint
	<p>β-human chorionic gonadotropin [β-HCG], lipid panel)</p> <ul style="list-style-type: none"> Assessment of vital sign measurements (Note: Weight is assessed as part of efficacy), 12-lead electrocardiogram (ECG) findings, and physical examination findings
Exploratory	
<ul style="list-style-type: none"> To compare the effects between the 2 treatment groups on patient-reported outcomes to diabetes medication and to further assess glycemic parameter, weight, and composite endpoints 	<ul style="list-style-type: none"> Patient-reported outcomes to diabetes medication at Baseline/Randomization, Week 10, and Week 26: <ul style="list-style-type: none"> Treatment-related impact measure for diabetes (TRIM-Diabetes) questionnaire Hypoglycemia fear survey-II (HFS-II) worry subscale Additional glycemic parameter, weight, and composite endpoints: <ul style="list-style-type: none"> HbA_{1c} change from Baseline at Week 26 by baseline FPG tertiles FPG change from Baseline at Week 26 by baseline FPG tertiles 24-hour glucose profile: 8-point self-monitored blood glucose (SMBG) profile at Baseline/Randomization, Week 10, and Week 26 (before and 120 minutes after the 3 main meals, at bedtime, and at 2 AM) Mean daily blood glucose based on the 8-point SMBG profile at Baseline/Randomization, Week 10, and Week 26 Number (and percentage) of subjects with ≤1 kg weight gain at Week 26 Percentage of subjects achieving HbA_{1c} <7.0% without weight gain and without hypoglycemia with blood glucose <56 mg/dL (<3.1 mmol/L) regardless of symptoms at Week 26 Proportion of subjects treated with once-weekly albiglutide that are able to totally replace or decrease prandial insulin without worsening HbA_{1c} control (worsening defined as >0.3% increase in HbA_{1c} compared with baseline HbA_{1c}) at Week 26
<ul style="list-style-type: none"> Analysis of genetic sampling may also be performed 	<ul style="list-style-type: none"> Genetic sampling

Objective	Endpoint
<ul style="list-style-type: none"> Analysis of novel biomarkers may also be performed 	<ul style="list-style-type: none"> Novel biomarker analysis may be performed; a decision on whether to analyze novel biomarker samples may be made after review of efficacy and safety endpoints at the end of the study or other emerging information that may become available during the study

Study Design

- This Phase IIIb, randomized, open-label, parallel-group, active-control, multicenter, treat-to-target study of 26 weeks' treatment duration will evaluate the efficacy and safety of once-weekly albiglutide as replacement of prandial insulin in subjects with T2DM.
- Subjects with inadequate glycemic control (glycosylated hemoglobin [HbA_{1c}] $\geq 7.0\%$ and $\leq 9.5\%$ at Screening) on their current basal-bolus insulin regimen (with or without metformin) despite at least 3 months of treatment will be recruited into the study. Subjects who achieve an HbA_{1c} value $\geq 7.0\%$ and $\leq 9.0\%$ following the Standardization Period will be randomized into the study.
- The intensification of basal-bolus insulin therapy (i.e., insulin glargine plus insulin lispro) according to predefined treat-to-target titration algorithms will serve as the active control.
- Subjects taking metformin as background antidiabetic medication will remain on their current dose for the duration of their participation in the study, unless a decline in kidney function results in a contraindication for metformin use.
- The study will comprise 4 study periods: Screening (2 weeks), Standardization (4 weeks), Treatment (26 weeks), and Posttreatment Follow-up (4 weeks). The total duration of a subject's participation will be approximately 36 weeks. Subjects will have 10 study center visits and approximately 18 telephone calls to monitor insulin titration.
- During the Screening Period (Week -6 through Week -5), subjects will provide written informed consent and undergo procedures to determine eligibility for study participation.
- After Screening, subjects meeting all eligibility criteria will enter a 4-week Standardization Period to transition from their current basal-bolus regimen to insulin glargine plus insulin lispro. Subjects already on insulin glargine plus insulin lispro will also enter the Standardization Period.
- During the Standardization Period, the basal-bolus insulin regimen may be adjusted to achieve glycemic targets as close to normal as possible without untoward hypoglycemia in accordance with product labeling in the respective country and standard of care at the study center.

- After the Standardization Period, subjects meeting additional criteria for randomization will be stratified by screening HbA_{1c} value (<8.0% versus ≥8.0%), age (<65 years versus ≥65 years), and current background metformin (metformin use versus no metformin use). Approximately 794 subjects will be randomly assigned in a 1:1 ratio such that
 - Approximately 397 subjects are randomly assigned to albiglutide + insulin glargine (with or without metformin)
 - Approximately 397 subjects are randomly assigned to intensification of insulin glargine + insulin lispro (with or without metformin)
- Randomized treatment assignment will be done via an interactive voice response system, and randomization will be implemented based on a sequestered fixed randomization schedule.
- Subjects in both the albiglutide plus insulin glargine and insulin glargine plus insulin lispro treatment groups will follow standardized insulin titration algorithms (separate algorithms for insulin glargine and insulin lispro) throughout the Treatment Period to achieve prespecified fasting and/or postprandial glucose targets.
- Dosing during the Treatment Period will be as described below:

Medication	Albiglutide + Insulin Glargine Group	Insulin Glargine + Insulin Lispro Group
Albiglutide	Baseline/Randomization: Start weekly SC injection at 30 mg. Week 4: Uptitrate to 50 mg weekly SC injection for the remainder of the Treatment Period.	None
Insulin lispro	Baseline/Randomization: Each insulin lispro dose will be downtitrated to half that used in the Standardization Period. ¹ Week 4: Stop insulin lispro for the remainder of the Treatment Period; insulin lispro may be re-introduced after Week 8 (See Section 5.1.3.5)	Baseline/Randomization: Continue at the same doses as at the end of the Standardization Period and adjust doses as per instructions in Section 5.1.3.2.
Insulin glargine	Continue at the same dose as at the end of the Standardization Period ¹ and adjust dose as per instructions in Section 5.1.3.2.	Continue at the same dose as at the end of the Standardization Period and adjust dose as per instructions in Section 5.1.3.2.
Metformin	Subjects will remain on their current dose for the duration of their participation in the study. ²	Subjects will remain on their current dose for the duration of their participation in the study. ²
Re-introduction of insulin lispro (if required)	After Week 8: See Section 5.1.3.5	Not applicable

SC = subcutaneous.

1. As described in Section 1.3.1, the risk of hypoglycemia is increased when albiglutide is used in combination with insulin; therefore, subjects may require a lower dose of insulin and should be monitored closely.
2. Unless a decline in kidney function results in a contraindication for metformin use. Metformin is to be stopped if the subject's estimated glomerular filtration rate, calculated according to the Modification of Diet in Renal Disease formula, decreases during the study to a level where metformin is contraindicated according to its label (as appropriate for each participating country).

- Subjects randomly assigned to treatment with albiglutide who continue to experience significant postprandial glucose excursions (i.e., >180 mg/dL [>10.0 mmol/L]) may have prandial insulin lispro re-introduced after Week 8 (i.e., 4 weeks after discontinuation of insulin lispro and up titration to albiglutide 50 mg) according to a standardized, stepwise approach.

Study Assessments

Efficacy Assessments

- HbA_{1c}
- FPG
- Body weight
- Hypoglycemia
- 8-point SMBG profile
- Daily insulin doses
- Weekly insulin injections
- TRIM-Diabetes questionnaire
- HFS-II worry subscale

Safety Assessments

- Hypoglycemic events
- AEs and SAEs
- Other AEs of special interest
- Pregnancy
- Clinical laboratory tests
- Vital sign measurements
- 12-lead ECGs
- Physical examinations

1. INTRODUCTION

1.1. Background

Diabetes affects an estimated 346 million people worldwide, with type 2 diabetes mellitus (T2DM) accounting for more than 90% of these cases [WHO, 2013; CDC, 2011]. The primary manifestation of this disease is chronic hyperglycemia, resulting from resistance to insulin action at a cellular and molecular level and a relative inadequacy in the secretion of endogenous insulin [ADA, 2012]. Chronic hyperglycemia has been firmly established as a key factor in the development of microvascular complications (retinopathy, nephropathy, and neuropathy) and to a lesser extent, macrovascular complications. The rapidly increasing incidence and prevalence of T2DM is a major worldwide healthcare issue due to increased patient morbidity and mortality and the costs associated with the management of these complications.

The intent of glycemia management in subjects with T2DM is to achieve normoglycemia and prevent the development of microvascular and macrovascular complications. The American Diabetes Association and the European Association for the Study of Diabetes recommend an individualized approach, targeting a glycosylated hemoglobin (HbA_{1c}) level of <7.0%, or as low as possible, without significant hypoglycemia or other adverse effects of treatment [Inzucchi, 2015; Inzucchi, 2012]. More stringent HbA_{1c} targets might be considered in selected patients; conversely, less stringent HbA_{1c} goals are appropriate for other patients such as those with a history of severe hypoglycemia, limited life expectancy, advanced complications, or extensive comorbid conditions.

The medical management of patients with T2DM consists of lifestyle interventions (i.e., diet, exercise, and weight reduction) together with oral antidiabetics (OADs), glucagon-like peptide-1 receptor (GLP-1R) agonists, or insulin therapy, as appropriate [Inzucchi, 2012]. Type 2 diabetes mellitus is a progressive disease characterized by worsening β -cell function over time. Patients will require higher doses and additional agents in an effort to achieve glycemic targets and many will require the addition of insulin to their treatment regimen to maintain glycemic control [Inzucchi, 2012]. Insulin therapy is commonly initiated with “basal” insulin typically administered as once-daily long-acting insulin analogues that aim to mimic the constant physiologic release of insulin that regulates metabolism and hepatic glucose production. When basal insulin alone fails to achieve appropriate glycemic targets, prandial insulin (administered as rapid-acting insulin analogues or regular insulin given with meals) is often added. Prandial insulin replacement is intended to mimic the postmeal insulin response to nutrient intake.

While insulin treatment is the cornerstone therapy for patients with T2DM that cannot be adequately controlled with OADs, insulin treatment fails to restore normal or near to normal glycemia in the majority of patients. Critical factors influencing the limitations of insulin therapy in T2DM include an increased risk of hypoglycemia, weight gain, failure to achieve consistent preprandial and postprandial glucose control, broad fluctuations in plasma glucose during the day, fear and discomfort among patients and physicians about these unintended effects, potential impact on quality of life, and poor treatment

compliance. Therefore, a clear unmet medical need remains for diabetes medications that restore glycemic control in patients on insulin therapy, without increasing the risks of hypoglycemia, weight gain, loss of quality of life, and poor compliance with treatment [Edelman, 2002].

Glucagon-like peptide-1 receptor agonists (e.g., exenatide, liraglutide, and lixisenatide) are therapeutic agents for the treatment of T2DM that stimulate insulin secretion in a glucose-dependent manner, suppress glucagon secretion with a low risk of hypoglycemia, delay gastric emptying, increase satiety, and are associated with modest weight reduction. The GLP-1R agonists lower fasting plasma glucose (FPG) levels and reduce postprandial glucose excursions. In addition, in preclinical models GLP-1R agonists stimulated transcription of genes important for glucose-dependent insulin secretion and promoted β -cell neogenesis [Gautier, 2005].

Albiglutide is a novel analogue of GLP-1 generated through a genetic fusion of 2 modified recombinant human GLP-1 molecules linked in tandem to the amino terminus of recombinant human albumin. Albiglutide has been developed for the treatment of T2DM as an adjunct to diet and exercise, as monotherapy, or in combination with existing therapies and has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In a Phase III clinical trial, albiglutide in combination with insulin glargine demonstrated an acceptable benefit:risk, controlling HbA_{1c} to target levels of <7.0% and <6.5%, providing clinically meaningful reductions in FPG, and favoring weight reduction with positive effects on the need for hyperglycemia rescue [GlaxoSmithKline Document Number 2011N126139_00; GlaxoSmithKline Document Number RM/2006/00602/07].

1.2. Rationale

The therapeutic aim of mealtime insulin is to blunt postprandial glycemic excursions, which can be extreme in some individuals, resulting in poor control during the day [Inzucchi, 2012]. Well-managed basal-bolus therapy provides a flexible way of controlling glucose throughout the day and night since dosing can be timed to approximate nondiabetic endogenous insulin release. However, in practice, basal-bolus insulin therapy is challenging to manage for both physicians and patients. Moreover, declining health and cognition tend to exacerbate the insulin management challenge in many older T2DM patients. In comparison to endogenous insulin, basal-bolus insulin therapy comes with a plethora of issues [Swinnen, 2009; McCoy, 2012; Hessler, 2014], such as

- Dose-dependent increased risk of hypoglycemia
- Dose-dependent increased mortality risk associated with hypoglycemia
- Increased risk of weight gain
- Encumbered quality of life associated with need to balance insulin dosing and carbohydrate intake, in both timing and magnitude

- Cost and stress of multiple daily injections
- Earlier loss of independence with aging due to the complexities of diabetes management with insulin

Treatments that diminish insulin demand and preserve or enhance β -cell function are expected to result in better glycemic control and diminished risk of these insulin therapy complications.

Combining a marketed GLP-1R agonist with basal insulin is part of the current treatment armamentarium for T2DM; however, none of these agents are currently indicated for use in product labeling with bolus insulin. Two studies have reported reductions in prandial insulin doses following the addition of exenatide with no major hypoglycemic events [Yoon, 2009; Viswanathan, 2007]. Liraglutide, when used in combination with a basal-bolus insulin regimen in patients with T2DM, allowed for a reduction in total and bolus insulin doses [Lane, 2014]. However, the Association of British Clinical Diabetologists' audit revealed a worsening of glycemic control for almost 50% of patients who stopped insulin therapy upon initiation of exenatide; thus, it is recommended that insulin be reduced but not discontinued once a significant glycemic improvement has been observed after initiating therapy with a GLP-1R agonist [Thong, 2011]. The difficulty of how fast and how far to downtitrate insulin doses without compromising glycemic control has been recognized in reviews of GLP-1R agonists [Holst, 2013] and is still an open question.

The Phase IIIa clinical development program for albiglutide included 2 studies with insulin, both open-label, the first comparing albiglutide with insulin glargine (Study GLP112754) and the second comparing albiglutide when added on to insulin glargine versus insulin lispro added on to insulin glargine (Study GLP108486). At their respective primary endpoints (Week 52 in Study GLP112754 and Week 26 in Study GLP108486), both studies showed that albiglutide was statistically noninferior to each insulin treatment approach with regard to HbA_{1c} and demonstrated that albiglutide could be used as an alternative to insulin therapy in patients with late-stage T2DM. Despite comparable glucose lowering, albiglutide therapy was associated with approximately 1.5- to 2-fold less symptomatic hypoglycemia and with weight loss rather than weight gain compared with the addition of insulin (treatment difference of 1.5 to 2.6 kg).

This study will evaluate the efficacy and safety of once-weekly albiglutide administered in combination with basal insulin as a replacement for bolus insulin in subjects with T2DM who are currently managed with a basal-bolus insulin regimen but who are not achieving glycemic treatment goals. It is expected that subjects switched to albiglutide plus basal insulin (with discontinuation of bolus insulin therapy) compared with those intensifying basal-bolus insulin therapy will be able to maintain glycemic control with less hypoglycemia and less weight gain, while also demonstrating a reduced total daily insulin requirement and reduced number of weekly injections (e.g., 28 injections per week [7 basal insulin and up to 21 bolus insulin injections] in basal-bolus-treated subjects compared with potentially 8 injections per week [1 weekly albiglutide injection and 7 basal injections] in subjects switching to basal insulin plus albiglutide).

Data from this study will support the concept that albiglutide is a potential alternative to bolus insulin that will simplify insulin therapy in subjects with T2DM that do not reach adequate control with basal-bolus therapy.

1.3. Benefit-to-Risk Assessment

Albiglutide has been evaluated in a comprehensive global program of studies involving approximately 9000 patient-years of overall exposure to date (including over 4000 patient-years of exposure to albiglutide), with 8 well-controlled Phase III studies (including 1 study in subjects with concurrent renal impairment), ranging in duration from 32 weeks to 3 years and using both 30-mg and 50-mg once-weekly dosing. This has permitted a robust assessment of efficacy, safety, and tolerability in a representative T2DM population that spanned newly diagnosed subjects treated with diet and exercise alone through subjects on background oral monotherapy, oral dual therapy, oral triple therapy, and basal insulin.

Summaries of findings from both clinical and nonclinical studies conducted with albiglutide can be found in the investigator's brochure (IB) [GlaxoSmithKline Document Number [RM/2006/00602/07](#); GlaxoSmithKline Document Number [2014N203025_00](#)], subsequent IB updates, and the product label. The following section outlines the risk assessment and mitigation strategy for this protocol.

1.3.1. Risk Assessment

Key risks (identified and potential) associated with the use of albiglutide, or the GLP-1R agonist class, as well as the mitigation strategy for key risks of clinical significance are provided in [Table 1](#). Please refer to the IB [GlaxoSmithKline Document Number [RM/2006/00602/07](#); GlaxoSmithKline Document Number [2014N203025_00](#)] and any subsequent IB updates for a thorough summary of the nonclinical and clinical experience with albiglutide as well as the complete guidance for the investigator (IB Section 6). In addition, the risks associated with study participation, study procedures, or comparators are also included in [Table 1](#).

Table 1 Risk Assessment for Albiglutide (GSK716155)

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: (albiglutide [GSK716155]) Identified Risks		
Pancreatitis [identified risk]	<p>In clinical trials, acute pancreatitis has been reported in association with albiglutide and other GLP-1R agonists (refer to Section 5.4.5.2 and Section 6 of the IB).</p> <p>Albiglutide has not been studied in subjects with a history of pancreatitis to determine whether these subjects are at increased risk for pancreatitis.</p>	<p>Specific eligibility and withdrawal criteria (see Section 4)</p> <p>Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects</p>
Gastrointestinal (GI) events [identified risks]	<p>Albiglutide has not been studied in subjects with severe GI disease, including severe gastroparesis.</p> <p>Use of albiglutide and other GLP-1R agonists may be associated with GI AEs (e.g., diarrhea, nausea, and vomiting) (refer to Section 5.4.5.4 and Section 6 of the IB).</p>	<p>Specific GI eligibility criteria (see Section 4)</p> <p>Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects</p>
Hypoglycemia [identified risk]	<p>Albiglutide's mechanism of action is associated with a low intrinsic risk of significant hypoglycemia; however, when used in combination with insulin secretagogues (such as SUs) or insulin, the risk of hypoglycemia is increased (refer to Section 5.4.5.1 and Section 6 of the IB).</p>	<p>Subjects on concurrent SU are excluded (see Section 4.2).</p> <p>Close monitoring for hypoglycemia and need for intervention via frequent contact with subjects who will self-monitor blood glucose (see Section 4.5 and Section 5.1.3.2)</p> <p>Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects</p>

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
<p>Immunogenicity (e.g., clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, other immune-related events)</p> <p>[identified risk]</p>	<p>In the Phase III program, approximately 5% of subjects developed anti-albiglutide antibodies, but based on available clinical data, anti-albiglutide antibody formation is not expected to impact the overall safety or efficacy of albiglutide treatment (refer to Section 5.6.1 of the IB).</p> <p>Although most subjects with injection site reactions were antibody negative (approximately 85%), injection site reactions were reported more frequently for antibody-positive subjects (approximately 41%) than antibody-negative subjects (approximately 14%).</p> <p>Hypersensitivity reactions are of potential concern with any injected protein and were reported rarely in the Phase III program (refer to Section 5.4.5.5 and Section 6 of the IB).</p>	<p>Specific eligibility and withdrawal criteria (see Section 4)</p> <p>Risk communication via informed consent form for subjects</p>
<p>Injection site reactions</p> <p>[identified risk]</p>	<p>Albiglutide is given as an SC injection in the abdomen, thigh, or upper arm and may cause rash, erythema, and/or itching at the injection site (IB Section 5.4.5.6).</p>	<p>Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects</p> <p>Subjects will be advised to use a different injection site each week.</p>
<p>Other adverse reactions (e.g., pneumonia, atrial fibrillation/atrial flutter, appendicitis, and hypersensitivity reactions)</p> <p>[identified risks]</p>	<p>In the Phase III program, other adverse reactions were observed with a cumulative incidence of <3% in studies up to 3 years in duration (Refer to Section 5.4.5.10, Section 5.4.5.11, and Section 6 of the IB).</p>	<p>Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects</p>

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: (albiglutide [GSK716155]) Potential Risks		
Thyroid C-cell tumors [potential risk]	<p>This potential risk arises from nonclinical rodent studies where GLP-1R agonists have been associated with increases in serum calcitonin, thyroid C-cell focal hyperplasia, and C-cell tumors. The relevance of these observations to humans is uncertain.</p> <p>In Phase III studies of up to 3 years in duration, albiglutide was not associated with clinically relevant increases in serum calcitonin (refer to Section 5.4.5.3 and Section 6 of the IB).</p>	<p>Subjects with a personal or family history of MTC or with multiple endocrine neoplasia syndrome type 2 are excluded (see Section 4.3).</p> <p>Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects</p>
Other malignant neoplasms (e.g., pancreatic cancer or malignancy when used in combination with insulin) [potential risks]	<p>Theoretical concern for pancreatic cancer associated with GLP-1–based therapies (DPP-IV inhibitors and GLP-1R agonists) is under evaluation by regulatory authorities [Egan, 2014] and has thus far concluded that a causal relationship cannot be established currently, but they will continue to investigate as more data become available.</p> <p>Theoretical concern raised by the European Union regulatory authorities is based on their concern for the biological plausibility of a tumor-promoting effect when a GLP-1 agonist is combined with insulin.</p>	Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects
Cardiovascular (CV) safety of antidiabetic therapy [potential risk]	<p>T2DM is associated with an elevated risk of CV disease. Global regulatory agencies require new antidiabetic therapies to demonstrate that the new therapy is not associated with an unacceptable increase in CV risk (refer to Section 5.4.5.8 of the IB).</p> <p>In the Phase III registration program, an independent Clinical Endpoint Committee prospectively adjudicated blinded CV events. The final CV meta-analysis showed no increased CV risk (MACE+ composed of CV death, MI, stroke, and hospitalization for unstable angina) with albiglutide versus all comparators (refer to Section 5.4.5.8 of the IB; MACE+ hazard ratio = 1.00; 95% CI: 0.68, 1.49).</p>	Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Hepatotoxicity [potential risk]	One subject in the Phase III clinical program developed a probable drug-induced liver injury with an asymptomatic elevation in ALT and total bilirubin, although the case had some atypical features and complicating factors (refer to Section 5.4.5.7 of the IB).	Specific eligibility and withdrawal criteria (see Section 4)
Investigational Product: (albiglutide [GSK716155]) Additional Considerations		
Patient population with severe renal impairment (eGFR <30 mL/min/1.73 m ²)	Experience in T2DM patients with severe renal impairment is very limited. Subjects with severe renal (eGFR <30 mL/min/1.73 m ²) impairment receiving albiglutide experienced a higher frequency of diarrhea, nausea, and vomiting compared with subjects with mild/moderate renal impairment (refer to Section 5.4.6 and Section 6 of the IB).	Subjects with severe renal impairment are excluded from this study (see Section 4.3). Specific monitoring guidance provided (see Section 5.1.1 and Section 6.3.5.1). Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects
Drug interactions	Albiglutide causes a delay in gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications (refer to Section 5.2.1.2, Section 5.2.5, and Section 6 of the IB). Drug interaction studies have been conducted with digoxin, warfarin, oral contraceptives, and simvastatin, which demonstrated no clinically relevant PK or PD effects.	Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects
Pregnancy and lactation	Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown (refer to Section 4.4.6 and Section 6 of the IB). It is not known if albiglutide is secreted into human milk during lactation. Given that albiglutide is an albumin-based protein therapeutic, it is likely to be present in human milk. Decreased body weight in offspring was observed in mice treated with albiglutide during gestation and lactation.	Specific eligibility and withdrawal criteria (see Section 4) Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects
Study Design or Procedures		
Standardization Period	Converting to insulin glargine and insulin lispro during the	Specific withdrawal criteria and monitoring guidelines (see

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	Standardization Period may result in glycemic excursions, potentially leading to hypoglycemic events or worsening hyperglycemia.	<p>Section 4.5.1 and Section 5.1.1)</p> <p>Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects</p> <p>The conversion from prior basal-bolus insulin regimen to insulin glargine and insulin lispro will be performed in a manner consistent with product labelling for each treatment (see Section 5.1.1).</p>
Potential risk for significant postprandial glucose excursions (i.e., >180 mg/dL [>10.0 mmol/L]) following discontinuation of insulin lispro in the once-weekly albiglutide treatment group	<p>Currently there are no accepted guidelines for downtitrating the total daily dose of insulin, particularly to guide the discontinuation of rapid-acting prandial insulin or the initiation of GLP-1R agonists in patients treated with basal-bolus insulin therapy.</p> <p>Per the protocol study design, subjects randomly assigned to the albiglutide treatment group will reduce insulin lispro by 50% at Baseline/Randomization, followed by complete (100%) discontinuation of insulin lispro at Week 4 (see Section 5.1.2).</p>	Subjects randomly assigned to the albiglutide treatment group who continue to experience significant postprandial glucose excursions (i.e., >180 mg/dL [>10.0 mmol/L]) may have prandial insulin lispro re-introduced after Week 8 (see Section 5.1.3.5).
Other		
Insulin glargine and insulin lispro	<p>Hypoglycemia is the most common adverse effect associated with the use of insulins. The risk of hypoglycemia increases with tighter glycemic control (refer to the product labels for insulin glargine and insulin lispro, respectively, [Lantus US Package Insert, 2013; Humalog US Package Insert, 2013]).</p> <p>Other less frequent important risks include hypersensitivity and allergic reactions, hypokalemia, weight gain, lipodystrophy following long-term administration, peripheral edema, and fluid retention and heart failure with concomitant use of PPAR-γ agonists.</p> <p>Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy.</p>	<p>Subject education on the signs and symptoms of hypoglycemia (including nocturnal hypoglycemia), common causes of hypoglycemia, appropriate methods to help prevent hypoglycemia, and on the self-treatment of hypoglycemic episodes (see Section 6.3.1)</p> <p>Close monitoring for hypoglycemia and need for intervention (e.g., insulin dose adjustment, withdrawal from study participation) via frequent contact with subjects, who will self-monitor blood glucose (see Section 4.5, Section 5.1.3.3, and Section 6.2.2)</p> <p>Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects</p>

Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.	

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

1.3.2. Benefit Assessment

The clinical data from the Phase IIIa development program show that once-weekly albiglutide treatment (both the 30- and 50-mg doses), in a single-dose pen device, results in clinically relevant lowering of HbA_{1c} and FPG in T2DM patients, when given as monotherapy and in combination with metformin, sulfonylurea (SU), thiazolidinedione, and basal insulin (refer to Section 5.5 of the IB) [GlaxoSmithKline Document Number [RM/2006/00602/07](#)]. Furthermore, the durability of the effect on these glycemic parameters has been shown over a study period of 3 years. Body weight decreased slightly or remained stable during treatment, which is of benefit considering that continuous weight gain is a clinical problem in this patient group. Maintaining body weight while decreasing HbA_{1c} is therefore considered a beneficial effect of importance.

As previously noted (see Section 1.1), the use of albiglutide in combination with insulin or in an active-controlled study versus insulin has been evaluated in separate clinical studies: 1 study comparing albiglutide with insulin glargine (Study GLP112754) and a second study comparing albiglutide with insulin lispro when added on to insulin glargine (Study GLP108486). In both of these studies, albiglutide was shown to be statistically noninferior to each insulin treatment approach with regard to HbA_{1c} at the primary endpoint (Week 52 in Study GLP112754 and Week 26 in Study GLP108486) and demonstrated that albiglutide could be used as an alternative to insulin therapy in patients with late-stage T2DM. Despite comparable glucose lowering, albiglutide therapy was associated with approximately 1.5- to 2-fold less symptomatic hypoglycemia and with weight loss rather than weight gain compared with the addition of insulin (treatment difference of 1.5 to 2.6 kg).

In this study, where albiglutide treatment will be added to a regimen of insulin glargine, subjects are expected to achieve similar benefits (reductions in HbA_{1c} and FPG with weight loss or weight remaining stable) as seen in the previous Phase III studies. Subjects in the albiglutide group will also receive fewer subcutaneous injections per week than subjects in the insulin lispro group (8 versus 28, respectively).

Subjects in the insulin glargine plus insulin lispro group will also be receiving effective antihyperglycemic medication, which will be titrated up or down to clinically relevant glycemic targets, and therefore these subjects should demonstrate reductions in HbA_{1c} and FPG, though weight gain may occur. Subjects may also receive the benefit of fewer injection site reactions and gastrointestinal (GI) events, based on the results from Study

GLP108486 (albiglutide versus insulin lispro, both added on to insulin glargine) where subjects in the insulin lispro plus insulin glargine treatment group experienced fewer such events than subjects in the albiglutide plus insulin glargine group.

Finally, as a result of participating in a clinical trial, each subject will receive more contact with the study center, have diet and exercise advice reinforced at each visit, and have more regular HbA_{1c} assessments than would be performed as part of their usual standard of care.

1.3.3. Overall Benefit-to-Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with albiglutide are justified by the anticipated benefits that may be afforded to subjects with T2DM.

Knowledge from this study will contribute to the overall benefit-to-risk profile of albiglutide. The results from this study may help physicians better understand T2DM, treatment for T2DM, which types of subjects are more likely to benefit from treatment with albiglutide, or which types of subjects are more likely to have side effects from albiglutide.

2. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
<ul style="list-style-type: none"> To evaluate the glycemic effectiveness of once-weekly albiglutide as replacement of prandial insulin in subjects with T2DM receiving basal-bolus insulin therapy 	<ul style="list-style-type: none"> Change from Baseline in HbA_{1c} at Week 26
Secondary	
<i>Key Secondary</i>	
<ul style="list-style-type: none"> To determine the proportion of subjects treated with once-weekly albiglutide that are able to replace prandial insulin without the need for re-introduction of insulin lispro 	<ul style="list-style-type: none"> Proportion of subjects treated with once-weekly albiglutide that are able to discontinue insulin lispro at Week 4 and do not meet prespecified criteria for severe, persistent hyperglycemia through Week 26
<ul style="list-style-type: none"> To demonstrate a significant difference in the frequency of hypoglycemic events between treatment groups 	<ul style="list-style-type: none"> Percentage of subjects with severe or documented symptomatic hypoglycemia through Week 26 (see Section 6.3.1)
<ul style="list-style-type: none"> To demonstrate a significant difference in body weight between treatment groups 	<ul style="list-style-type: none"> Change from Baseline in body weight at Week 26 and over time
<ul style="list-style-type: none"> To demonstrate a significant reduction in total daily dose of insulin between treatment groups 	<ul style="list-style-type: none"> Total daily insulin dose at Week 26

Objective	Endpoint
	<i>Supportive Secondary</i>
<ul style="list-style-type: none"> To assess additional glycemic parameters, achievement of HbA_{1c} treatment goals, body weight, and total daily insulin dose 	<ul style="list-style-type: none"> Additional glycemic parameters: <ul style="list-style-type: none"> HbA_{1c} change from Baseline over time FPG change from Baseline at Week 26 and over time Achievement of HbA_{1c} treatment goals: <ul style="list-style-type: none"> Proportion of subjects achieving a HbA_{1c} <7.0% at Week 26 and over time Proportion of subjects achieving a HbA_{1c} <6.5% at Week 26 and over time Incidence and time to meeting prespecified criteria for severe, persistent hyperglycemia at Week 26 Additional assessments of daily insulin doses: <ul style="list-style-type: none"> Total daily insulin dose (24-hour total international units [IU] and total units/kg body weight) over the 3 days preceding the Baseline/Randomization and Week 4, 10, and 18 visits Total daily basal insulin (insulin glargine) (24-hour total IU and total units/kg body weight) over the 3 days preceding the Baseline/Randomization and Week 4, 10, 18, and 26 visits Total daily bolus insulin (insulin lispro) (24-hour total IU and total units/kg body weight) over the 3 days preceding the Baseline/Randomization and Week 4, 10, 18, and 26 visits Total number of weekly insulin injections (7 days) to achieve glycemic control at Baseline/Randomization and Week 4, 10, 18, and 26 Composite endpoints (after 26 weeks of treatment): <ul style="list-style-type: none"> Percentage of subjects achieving HbA_{1c} <7.0% without weight gain Percentage of subjects achieving HbA_{1c} <7.0% without severe or documented symptomatic hypoglycemia Percentage of subjects achieving HbA_{1c} <7.0% without weight gain and without severe or documented hypoglycemia

Objective	Endpoint
<ul style="list-style-type: none"> To evaluate the safety and tolerability of the 2 treatment groups 	<ul style="list-style-type: none"> Adverse events (AEs) and serious AEs (SAEs), including AEs and SAEs leading to discontinuation of randomized study medication Other AEs of special interest (for example, cardiovascular [CV] events, GI events, injection site reactions, potential systemic allergic reactions, pancreatitis, pancreatic cancer, medullary thyroid cancer, malignant neoplasms following treatment with insulin, diabetic retinopathy events, appendicitis, liver events, pneumonia, and atrial fibrillation/flutter) Assessments of hypoglycemia: <ul style="list-style-type: none"> Percentage and number of events of hypoglycemia with confirmed home blood glucose monitoring and/or third-party intervention through Week 26 (i.e., severe, documented symptomatic, and asymptomatic hypoglycemic events, see Section 6.3.1) in 3-month intervals (i.e., from Baseline/Randomization to Week 12, >Week 12 to Week 26) Incidence of hypoglycemic events (in total and by each category as defined by the American Diabetes Association criteria) Incidence of daytime hypoglycemia (in total and by category), defined as hypoglycemic events with an onset between 06:00 hours and 00:00 hours (inclusive), and nocturnal hypoglycemia (in total and by category), defined as hypoglycemic events with an onset between 00:01 hours and 05:59 hours (inclusive) Incidence of hypoglycemia with blood glucose <56 mg/dL (<3.1 mmol/L), regardless of symptoms Assessment of clinical laboratory tests (hematology, clinical chemistry, urinalysis, β-human chorionic gonadotropin [β-HCG], lipid panel) Assessment of vital sign measurements (Note: Weight is assessed as part of

Objective	Endpoint
	efficacy), 12-lead electrocardiogram (ECG) findings, and physical examination findings
Exploratory	
<ul style="list-style-type: none"> To compare the effects between the 2 treatment groups on patient-reported outcomes to diabetes medication and to further assess glycemic parameter, weight, and composite endpoints 	<ul style="list-style-type: none"> Patient-reported outcomes to diabetes medication at Baseline/Randomization, Week 10, and Week 26: <ul style="list-style-type: none"> Treatment-related impact measure for diabetes (TRIM-Diabetes) questionnaire Hypoglycemia fear survey-II (HFS-II) worry subscale Additional glycemic parameter, weight, and composite endpoints: <ul style="list-style-type: none"> HbA_{1c} change from Baseline at Week 26 by baseline FPG tertiles FPG change from Baseline at Week 26 by baseline FPG tertiles 24-hour glucose profile: 8-point self-monitored blood glucose (SMBG) profile at Baseline/Randomization, Week 10, and Week 26 (before and 120 minutes after the 3 main meals, at bedtime, and at 2 AM) Mean daily blood glucose based on the 8-point SMBG profile at Baseline/Randomization, Week 10, and Week 26 Number (and percentage) of subjects with ≤ 1 kg weight gain at Week 26 Percentage of subjects achieving HbA_{1c} <7.0% without weight gain and without hypoglycemia with blood glucose <56 mg/dL (<3.1 mmol/L) regardless of symptoms at Week 26 Proportion of subjects treated with once-weekly albiglutide that are able to totally replace or decrease prandial insulin without worsening HbA_{1c} control (worsening defined as >0.3% increase in HbA_{1c} compared with baseline HbA_{1c}) at Week 26
<ul style="list-style-type: none"> Analysis of genetic sampling may also be performed 	<ul style="list-style-type: none"> Genetic sampling
<ul style="list-style-type: none"> Analysis of novel biomarkers may also be performed 	<ul style="list-style-type: none"> Novel biomarker analysis may be performed; a decision on whether to analyze novel biomarker samples may be made after review of efficacy and safety

Objective	Endpoint
	endpoints at the end of the study or other emerging information that may become available during the study

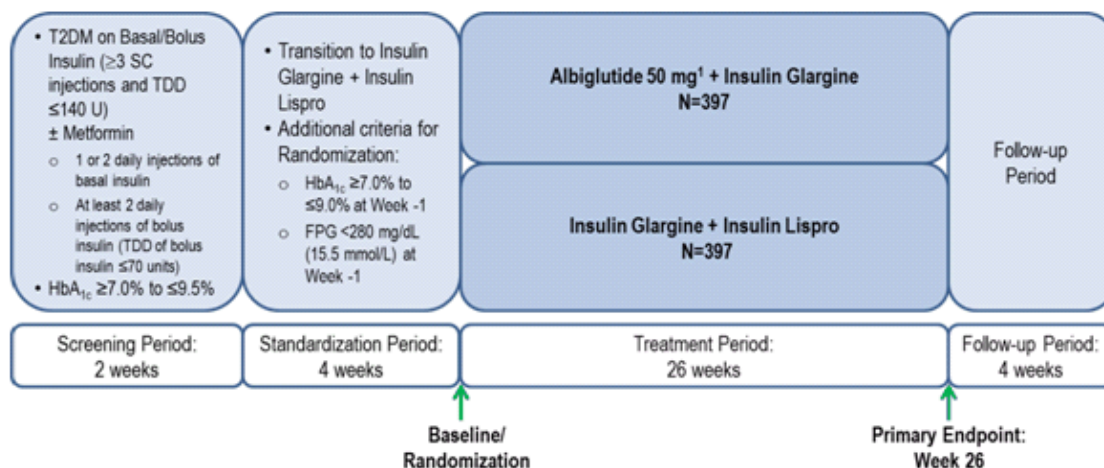
3. INVESTIGATIONAL PLAN

3.1. Study Design

This Phase IIIb, randomized, open-label, parallel-group, active-control, multicenter, treat-to-target study of 26 weeks' treatment duration will evaluate the efficacy and safety of once-weekly albiglutide as replacement of prandial insulin in subjects with T2DM failing to achieve adequate glycemic control on their current basal-bolus insulin regimen (with or without metformin). In this study, the intensification of basal-bolus insulin therapy (i.e., insulin glargine plus insulin lispro) according to predefined treat-to-target titration algorithms will serve as the active control.

The study will comprise 4 study periods (Figure 1): Screening (2 weeks), Standardization (4 weeks), Treatment (26 weeks), and Posttreatment Follow-up (4 weeks). The total duration of a subject's participation will be approximately 36 weeks.

Figure 1 Study Design



SC = subcutaneous; T2DM = type 2 diabetes mellitus; TDD = total daily dose.

Note: Subjects on metformin will continue on the same dose throughout the study, except if the subject's estimated glomerular filtration rate, calculated according to the Modification of Diet in Renal Disease formula, decreases during the study to a level where metformin is contraindicated according to its label (as appropriate for each participating country), in which case metformin is to be stopped.

1. At Baseline/Randomization, albiglutide will be started at 30 mg once weekly with uptitration to albiglutide 50 mg once weekly at Week 4. Subjects randomly assigned to this treatment group will reduce insulin lispro by 50% at Baseline/Randomization, followed by complete (100%) discontinuation of insulin lispro at Week 4.

During the Screening Period (Week -6 through Week -5), subjects will provide written informed consent and undergo procedures to determine eligibility for study participation.

Note: A fasting HbA_{1c} value may be determined using a Metrika kit (Metrika, Inc, Sunnyvale, California) or other finger-stick procedure to provide an initial guide of subject eligibility for investigators. The test is not required. The HbA_{1c} value obtained at this screening visit is to be used as a guide for the investigator. If the investigator feels that a subject is a good candidate for the study, the subject should continue with the screening visit and have HbA_{1c} assessed through the central laboratory. The central laboratory measure will serve as the official HbA_{1c} value to determine subject eligibility for entry into the Standardization Phase.

After Screening, subjects meeting all eligibility criteria will enter a 4-week Standardization Period to transition from their current basal-bolus regimen to insulin glargine plus insulin lispro. Subjects already on insulin glargine plus insulin lispro will also enter the Standardization Period. During the Standardization Period, the basal-bolus insulin regimen may be adjusted to achieve glycemic targets as close to normal as possible without untoward hypoglycemia in accordance with product labeling in the respective country and standard of care at the study center. Subjects will also receive training on the use of albiglutide injector pens and sterile techniques for self-administration in preparation for the Treatment Period, during which the investigational product (albiglutide) will be administered at home. See Section 5.1 for further details.

After the Standardization Period, subjects meeting additional criteria for randomization will be stratified by screening HbA_{1c} value (<8.0% versus ≥8.0%), age (<65 years versus ≥65 years), and current use of background metformin (metformin use versus no metformin use). Approximately 794 subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio such that

- Approximately 397 subjects are randomly assigned to albiglutide + insulin glargine (with insulin lispro discontinuation at Week 4) (with or without metformin)
- Approximately 397 subjects are randomly assigned to intensification of insulin glargine + insulin lispro (with or without metformin)

In this treat-to-target study, subjects in both the albiglutide plus insulin glargine and insulin glargine plus insulin lispro treatment groups will follow standardized insulin titration algorithms (separate algorithms for insulin glargine and insulin lispro) throughout the Treatment Period to achieve prespecified fasting and/or postprandial glucose targets; see Section 5.1.3.2. The treat-to-target study design should equalize glycemic efficacy between the treatment groups, thus allowing for comparison of other measures of clinical utility (e.g., differences in hypoglycemia, body weight, total daily dose of insulin, number of injections per week, and patient-reported outcomes).

Subjects randomly assigned to treatment with albiglutide who continue to experience significant postprandial glucose excursions (i.e., >180 mg/dL [>10.0 mmol/L]) may have prandial insulin lispro re-introduced after Week 8 (i.e., 4 weeks after discontinuation of insulin lispro and uptitration to albiglutide 50 mg) according to a standardized, stepwise approach. See Section 5.1.3.5 for further details.

Subjects will have 10 study center visits (Table 5) and approximately 18 telephone calls (Table 6) to monitor and adjust insulin glargine and insulin lispro doses.

Potential events of pancreatitis will be adjudicated by an independent pancreatitis adjudication committee (PAC).

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

With respect to the study conduct, subject completion is defined as completion of all periods of the study up to and including the Follow-up visit. For the primary analysis, subject completion is defined as completion of all periods of the study up to and including the Treatment Period.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables, are essential and required for study conduct.

There will be no compassionate use of study medication once a subject completes or withdraws early from the study.

3.2. Discussion of Design

3.2.1. Choice of Control

Due to the progressive β -cell dysfunction that characterizes T2DM, many patients will eventually require insulin replacement therapy. Unless the patient is markedly hyperglycemic, initial insulin therapy is typically “basal” insulin alone [Holman, 2009]. Basal insulin (such as neutral protamine Hagedorn, insulin glargine, insulin detemir, or insulin degludec) provides relatively uniform insulin coverage throughout the day and night, mainly to control blood glucose by suppressing hepatic glucose production in between meals and during sleep. Although the majority of patients with T2DM requiring insulin therapy can be successfully treated with basal insulin alone, some will require prandial insulin therapy due to low functional β -cell mass, high insulin resistance, or both. Prandial insulins are shorter-acting insulins (such as regular insulin, insulin lispro, insulin aspart, or insulin glulisine), which may be dosed just before the meal (i.e., “bolus” insulin therapy). The control group in this study will utilize a basal-bolus regimen, the current standard of care. In this treat-to-target study, the active control group will be intensification of insulin glargine + insulin lispro according to predefined titration algorithms.

3.2.2. Duration of Treatment

Albiglutide has demonstrated efficacy in T2DM subjects, as monotherapy and in combination with existing antidiabetic medication, in Phase III studies of various duration ranging from 32 weeks to 156 weeks. This Phase IIIb study, with a treatment

period of 26 weeks is sufficient to assess the primary, secondary, and safety endpoints of the study and is consistent with regulatory authority recommendations for evaluating efficacy and safety in patients with T2DM [FDA Guidance for Industry, 2008; EMA Guidance, 2012].

3.2.3. Intention of Standardization Period

Standardizing the type and frequency of basal and bolus insulin during this period is important to decrease the confounding variability associated with multiple combinations of insulins that would add substantial complexity to the insulin titration algorithms, thus complicating the interpretation of study results. The intent of the 4-week Standardization Period is to allow subjects to transition from their current basal insulin and bolus insulin to insulin glargine and insulin lispro (if not already taking them) and achieve a level of familiarity with this combination prior to randomization.

3.2.4. Dose of Albiglutide

Data from the 8 Phase III studies (Studies GLP108486, GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP114179, and GLP114130) confirmed that albiglutide 30-mg and 50-mg doses both showed robust efficacy and safety. Although a 30-mg dose of albiglutide is effective at controlling glycemia for at least 2 years in many subjects, an increase in dose to 50 mg weekly offers additional benefit, as demonstrated in Study GLP112756 and Study GLP114179. In other Phase III studies (Studies GLP108486, GLP112754, GLP112757, and GLP112753), the dose of albiglutide was increased to 50 mg according to clinical need, reflecting “real world” practice; this titration occurred in 69% of subjects during the period up to the primary endpoint in each study and confirmed the benefit of albiglutide uptitration. Importantly, the improvements in glycemic parameters after increasing to 50 mg albiglutide weekly occurred across all the concurrent background antidiabetic therapies included in the albiglutide studies (i.e., Study GLP108486 in which albiglutide was added on to insulin glargine [\pm OAD agents] and compared with insulin lispro added to insulin glargine [\pm OADs] and Study GLP112754 in which albiglutide was compared with insulin glargine in subjects failing on background metformin \pm SU). The 50-mg dose of albiglutide therefore provides additional glycemic benefit without significant safety issues, as shown in Study GLP112756 in which there was both a 30-mg treatment arm and a 50-mg treatment arm (30 mg for 12 weeks followed by uptitration to 50 mg) and in the 4 optional uptitration Phase III studies, where the data suggested no dose response that was likely to meaningfully impact the safety or tolerability profile.

The albiglutide dose in this study will start at 30 mg weekly and be increased to 50 mg weekly at Week 4. Therefore, this schedule will allow for a more homogeneous comparison of albiglutide (at 1 dose) to insulin lispro versus an individualized optional uptitration scheme based on glycemic thresholds (as in 4 of the Phase III studies), where uptitration occurred at various times during the study (as needed) and resulted in a mix of both 30-mg and 50-mg doses.

3.2.5. Insulin Doses

The starting dose for basal insulin (insulin glargine) in the Standardization Period should be the same (or 20% lower if the subject enters the study on 2 doses of basal insulin), on a unit-for-unit basis, as that taken by the subject during Screening; see Section 5.1.1 for additional details.

The starting dose for bolus insulin (insulin lispro) in the Standardization Period should be the same, on a unit-for-unit basis, as that taken by the subject during Screening; see Section 5.1.1 for additional details and guidance regarding permitted changes at the discretion of the investigator.

During the Treatment Period, the study will allow individualization of the insulin dose in both treatment groups (i.e., insulin glargine in the albiglutide treatment group and both insulin glargine and insulin lispro in the basal-bolus treatment group), with a treat-to-target approach and a titration regimen based on SMBG values and other important information, such as hypoglycemia (Table 3 and Table 4).

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

A sufficient number of subjects will be screened to randomly assign approximately 794 subjects. Assuming that 15% of subjects will withdraw early or be lost to follow-up, approximately 674 evaluable subjects (approximately 337 subjects per treatment group) are required to complete the study.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number RM/2006/00602/07; GlaxoSmithKline Document Number 2014N203025_00], any subsequent IB updates, and the package inserts for insulin glargine, insulin lispro, and metformin. See Section 5.1 for details.

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

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Male or female, 18 to 75 years of age (inclusive at the time of Screening) with T2DM
2. $HbA_{1c} \geq 7.0\%$ and $\leq 9.5\%$ at Screening. If the first screening HbA_{1c} does not meet the eligibility criterion, the HbA_{1c} value may be checked up to 2 times during Screening,

and if the average of these determinations meets the criterion, the subject may be eligible for further participation in the study

3. Currently treated with a basal-bolus insulin regimen (with or without metformin) for at least 3 months before Screening. The subject must be taking the following:
 - Basal insulin (1 or 2 daily injections of neutral protamine Hagedorn insulin, insulin glargine, insulin detemir, or insulin degludec)

AND

- Bolus insulin (at least 2 injections of regular insulin, insulin glulisine, insulin aspart, or insulin lispro) with a total daily dose of bolus insulin ≤ 70 units
- In addition, the total daily dose of insulin must be ≤ 140 units
- If taking metformin, a stable dose for at least 8 weeks before Screening

Note: Subject should not have received any other antidiabetic medication within 30 days before Screening (e.g., GLP-1R agonist, dipeptidyl peptidase-IV inhibitor, SU, meglitinide, sodium-glucose transporter 2 inhibitor, or thiazolidinedione). Subjects receiving commercially available premixed basal and prandial insulin are not eligible for this study.

4. Fasting C-peptide ≥ 0.8 ng/mL (≥ 0.26 nmol/L). If the fasting C-peptide is < 0.8 ng/mL (< 0.26 nmol/L) but stimulated C-peptide 90 minutes after a standardized mixed meal is ≥ 1.5 ng/mL (≥ 0.5 nmol/L), the subject may be eligible for further participation in the study [Jones, 2013; Maldonado, 2005]

Note: Plasma glucose will also be measured 90 minutes after the standardized mixed meal; if the concurrent plasma glucose collected 90 minutes after the standardized mixed meal is not ≥ 144.0 mg/dL (≥ 8.0 mmol/L), the stimulated C-peptide test may be repeated during an unscheduled visit.

5. Body mass index ≤ 40 kg/m²
6. Thyroid-stimulating hormone (TSH) level is normal or clinically euthyroid as demonstrated by further thyroid tests (e.g., free T4)
7. Female subjects of childbearing potential (i.e., not surgically sterile and/or not postmenopausal) must be practicing adequate contraception (as defined below) for the duration of participation in the study including the 4-week Posttreatment Follow-up Period
 - Abstinence from penile-vaginal intercourse, when this is the female's preferred and usual lifestyle
 - Oral contraceptive, either combined or progestogen alone
For subjects participating at sites in Germany: progestogen-only pills are only acceptable if they have a Pearl Index of less than 1.0 (e.g., those containing 75 µg desogestrel)
 - Injectable progestogen

- Implants of etonogestrel or levonorgestrel
 - Estrogenic vaginal ring
 - Percutaneous contraceptive patches
 - Intrauterine device or intrauterine system that has a failure rate of less than 1% per year when used consistently and correctly as stated in the product label
 - Male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject. The information on the male sterility can come from the site personnel's review of the female subject's medical records, medical examination of the subject and/or semen analysis, or interview with the female subject on her male partner's medical history.
 - Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007]
8. Willing and able to comply with all study procedures including performance of frequent SMBG profiles and use of an e-diary according to the protocol
 9. Able and willing to provide written informed consent after a thorough explanation of the study by the investigator or designee, which will include the opportunity for the subjects to ask questions
 10. Suitable for participation in a treat-to-target study, including intensified basal-bolus insulin therapy utilizing the prespecified glycemic targets defined in the protocol

4.3. Exclusion Criteria

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

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Type 1 diabetes mellitus
2. History of cancer that has not been in full remission for at least 3 years before Screening. (A history of squamous cell or basal cell carcinoma of the skin or treated cervical intra-epithelial neoplasia I or II is allowed)
3. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2
4. Current symptomatic biliary disease or history of acute or chronic pancreatitis
5. Severe gastroparesis, i.e., requiring regular therapy within 6 months before Screening
6. History of significant GI surgery that in the opinion of the investigator is likely to significantly affect upper GI or pancreatic function (e.g., gastric bypass and banding, antrectomy, Roux-en-Y bypass, gastric vagotomy, small bowel resection, or surgeries thought to significantly affect upper GI function)

7. History of hypoglycemia unawareness (i.e., the absence of autonomic warning symptoms before the development of neuroglycopenic symptoms such as blurred vision, difficulty speaking, feeling faint, difficulty thinking, and confusion)
8. Diabetic complications (e.g., active proliferative retinopathy or severe diabetic neuropathy) or any other clinically significant abnormality (including a psychiatric disorder) that, in the opinion of the investigator, may pose additional risk in administering the investigational product
9. Clinically significant CV and/or cerebrovascular disease within 3 months before Screening including, but not limited to, the following:
 - Stroke or transient ischemic attack
 - Acute coronary syndrome (myocardial infarction [MI] or unstable angina not responsive to nitroglycerin)
 - Cardiac surgery or percutaneous coronary procedure
10. Any history of New York Heart Association class III or IV heart failure
11. Alanine aminotransferase (ALT) $>2.5 \times$ upper limit of normal (ULN) or bilirubin $>1.5 \times$ ULN (isolated bilirubin $>1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin $<35\%$)
12. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). (Chronic stable hepatitis B and C are acceptable if subject otherwise meets entry criteria and is not on active antiviral treatment [e.g., presence of hepatitis B surface antigen or positive hepatitis C test result within 3 months of Screening])
13. Hemoglobin <11 g/dL (<110 g/L) for male subjects and <10 g/dL (<100 g/L) for female subjects at Screening
14. Estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m² (calculated using the Modification of Diet in Renal Disease [MDRD] formula) at Screening

Note: As the use of metformin in subjects with varying degrees of renal function may differ from country to country, use of metformin should be in accordance with the metformin product label within the participating country.
15. Fasting triglyceride level >750 mg/dL at Screening
16. Hemoglobinopathy that may affect proper interpretation of HbA_{1c}
17. Known allergy to albiglutide or any product components (including yeast and human albumin), any other GLP-1 analogue, insulin, or other study medication's excipients OR other contraindications (per the prescribing information) for the use of potential study medications (e.g., insulin glargine, insulin lispro)
18. Use of oral or systemically injected glucocorticoids within the 3 months before randomization or high likelihood of a requirement for prolonged treatment (>1 week) in the 6 months following randomization. However, short courses of oral steroids (single dose or multiple doses for up to 7 days) may be permitted provided these

cases are discussed with the medical monitor. Inhaled, intra-articular, epidural, and topical corticosteroids are allowed

19. Female subject is pregnant (confirmed by laboratory testing) or lactating
20. Receipt of any investigational drug within the 30 days or 5 half-lives, whichever is longer, before Screening, a history of receipt of an investigational antidiabetic drug within the 3 months before randomization, or receipt of albiglutide in previous studies

The following additional exclusion criteria apply for subjects participating at sites in Germany:

21. Persons who have been put in an institution because of official or legal order
22. Employees (or the employee's relatives) of the sponsor, the contract research organization, or the investigative site, including the investigator or other site staff

4.4. Additional Inclusion Criteria for Randomization

Subjects eligible for randomization in the study must meet the following additional criteria:

- $HbA_{1c} \geq 7.0\%$ and $\leq 9.0\%$ at Week -1. If the subject does not qualify for randomization based on this criterion, the assessment may be repeated on a weekly basis for a maximum of 2 additional weeks before randomization. The mean of all HbA_{1c} assessments (Week -1 plus the additional HbA_{1c} assessments) must be $\geq 7.0\%$ and $\leq 9.0\%$ for the subject to be eligible for randomization (see Section 4.6). Note: If a subject has confirmed (by a central laboratory) $HbA_{1c} < 7.0\%$ or $> 9.0\%$ at Week -1 or the subject decides not to continue repeat testing, he or she will be considered a standardization failure (see Section 4.6)
- $FPG < 280$ mg/dL (15.5 mmol/L) at Week -1 (by a blood glucose meter at the site and confirmed by a central laboratory). If the subject does not qualify for randomization based on this criterion, the assessment may be repeated on a weekly basis for a maximum of 2 additional weeks before randomization. The mean of all FPG assessments (Week -1 plus the additional FPG assessments) must be < 280 mg/dL (15.5 mmol/L) for the subject to be eligible for randomization (see Section 4.6). Note: If a subject has confirmed (by a central laboratory) $FPG \geq 280$ mg/dL (15.5 mmol/L) at Week -1 or the subject decides not to continue repeat testing, he or she will be considered a standardization failure (see Section 4.6)

4.5. Withdrawal Criteria

Every effort should be made to keep subjects in the study. The reasons for subjects not completing the study will be recorded.

The following **will** require withdrawal from the study:

- AE, which, in the opinion of the investigator precludes effective participation of the subject or poses a safety concern
- Elevation of liver function test results meeting any of the liver stopping criteria (see Section 6.3.6)
- Severe allergic/hypersensitivity reaction that is considered by the investigator to be attributable to randomized study medication or without a likely alternative etiology (see Section 6.3.9.3)
- Confirmed acute or chronic pancreatitis (see Section 6.3.9.4)
- Confirmed medullary thyroid cancer (see Section 6.3.9.6)
- Recurrent severe hypoglycemia or recurrent nocturnal hypoglycemia during the Treatment Period posing a potential risk to the subject, as judged by the investigator
- Pregnancy or intention of becoming pregnant
- Major protocol deviation if withdrawal from the study is mandated by the medical monitor (the investigator should discuss the protocol deviation with the medical monitor before withdrawing study medication)
- GSK-defined Sentinel Event. The medical monitor will advise the investigator if an SAE meets the criteria of a true Sentinel Event (e.g., without a clear alternate etiology) for which withdrawal is required (see Section 6.3.7.3)

In addition, a subject may be withdrawn from the study for the following reasons:

- FPG >270 mg/dL (15.0 mmol/L) at least 8 weeks after randomization on 3 consecutive days (by blood glucose meter), which is confirmed by a central laboratory (to be done within 2 weeks of the home glucose monitoring). Continuation of the subject will be at the discretion of the investigator after consultation with the medical monitor
- Lost to follow-up
- Study closed/terminated or investigator site closed (where subject transfer to another site is not possible)
- Subject decision (reason to be documented in the electronic case report form [eCRF], if specified by the subject)
- Investigator discretion

Note: Use of a prohibited medication constitutes a protocol deviation. Continuation of the subject in the study will be discussed with the medical monitor, and the decision of continuation or withdrawal will be documented.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the

rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

The half-life of albiglutide is approximately 5 days, and significant therapeutic concentrations can persist for 3 to 4 weeks after discontinuation. Therefore, the investigator should use caution when prescribing treatment after the withdrawal of active study medication, taking into consideration the long half-life of albiglutide. Thereafter, postwithdrawal treatments may be modified over time, as needed, at the investigator's discretion.

Study medication withdrawal will require withdrawal from the study. Withdrawn subjects will not be replaced.

4.5.1. Early Withdrawal Visit

Subjects who discontinue active participation in the study will no longer receive the randomized study medication. Immediately upon discontinuation from active participation in this study, these subjects should complete the early withdrawal treatment assessments and return for follow-up assessments 4 weeks later (Table 5). If the subjects are unable or unwilling to return for the follow-up assessments, GSK/PPD will make every effort to follow-up with the subjects or their physician or caregiver.

4.6. Screening/Standardization Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet all inclusion (Section 4.2) and exclusion (Section 4.3) criteria to continue in Screening. Subjects failing to meet eligibility criteria may be rescreened after 2 weeks, as appropriate. In order to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities, a minimal set of screen failure information will be collected including demography, screen failure details, eligibility criteria, and any SAEs.

Standardization failures are defined as subjects who begin the Standardization Period but do not complete the Standardization Period or subsequently fail the Additional Inclusion Criteria for Randomization (Section 4.4), or subjects who decide not to continue repeat testing. Standardization failures may not be rescreened.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

All medications used in this study will be open-label. Albiglutide, insulin glargine, and insulin lispro will be provided for use in this study. Other background antidiabetic medication, e.g., metformin (if used) will not be provided by GSK.

Albiglutide

Albiglutide is provided as a fixed-dose, fully disposable pen injector system for delivery of the investigational product from a prefilled dual chamber glass cartridge that is an integral part of the pen. It is intended for single use by the subject. The pen is designed for manual reconstitution of the dose, priming and insertion of the pen needle, and manual injection by the subject.

Albiglutide is intended for self-administration as a subcutaneous injection in the abdomen, thigh, or upper arm region. The pen includes a mechanical locking system that prevents the user from manipulating the dose button before the cartridge has been fully reconstituted. Reconstitution is performed through rotation of the pen housing parts. The pen is designed to work with standard pen needles.

When the injector pen product is reconstituted by the subject, a neutral, isotonic solution is produced. The pen delivers either 30 mg of albiglutide or 50 mg of albiglutide in a 0.5-mL injection volume.

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

Under normal conditions of handling and administration, albiglutide is not expected to pose significant safety risks to site personnel. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A material safety data sheet describing the occupational hazards and recommended handling precautions will be provided to site personnel if required by local laws or will otherwise be available from GSK upon request.

Albiglutide must be stored in a secure area at 2°C to 8°C and protected from freezing. Each site must maintain a temperature log. Access to albiglutide will be limited to the investigator and authorized site staff. Albiglutide must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Insulin Glargine and Insulin Lispro

Insulin glargine and insulin lispro injection pens for subcutaneous injection will be provided to all subjects, as appropriate, for the Standardization and Treatment Periods. Subjects will be instructed on the use and storage requirements for insulin glargine and

insulin lispro and will administer insulin glargine or insulin lispro as prescribed by their physician and in accordance with the package insert.

Insulin glargine should be self-administered as a subcutaneous injection once daily at bedtime in the abdomen, thigh, or upper arm region, and the injection sites rotated within a given injection area from 1 injection to the next.

Insulin lispro should be self-administered shortly before meals or, when necessary, soon after meals by subcutaneous injection in the upper arms, thighs, buttocks, or abdomen. Use of injection sites should be rotated so that the same site is not used more than approximately once per month. After injection, the site of injection should not be massaged.

Procedures for the disposal of unused study medication will be provided in the SPM.

5.1.1. Dosing Guidance During the Standardization Period

Subjects will transfer from their basal-bolus therapy at the end of Screening to insulin glargine plus insulin lispro as detailed below. Subjects already on once-daily bedtime insulin glargine and meal-time insulin lispro will also enter the Standardization Period.

Weekly telephone calls (if there is no scheduled study visit) must take place between the investigator and subject for the entire Standardization Period (Week -4 through Week -1) in order to make any needed insulin glargine or insulin lispro dose adjustments.

Insulin glargine

- If the subject's prestudy basal insulin is a once-daily regimen, transfer the subject to insulin glargine (subcutaneous injection) once daily at bedtime on a unit-per-unit basis. Note: At the discretion of the investigator, it is permissible to reduce the insulin glargine dose by up to 10%.
- If the subject's prestudy basal insulin is given twice daily, then the subject's insulin glargine should be started once daily at bedtime at a dose that is 20% lower than the total daily prestudy basal dose.

During the Standardization Period, insulin glargine may be adjusted to achieve glycemic targets as close to normal as possible without untoward hypoglycemia in accordance with product labeling in the respective country and standards of care at the study center. The treat-to-target titration algorithm for insulin glargine (Section 5.1.3.2, Table 3) is intended for use only during the Treatment Period.

Insulin lispro

- If the subject's current regimen of bolus insulin is administered at each of the 3 main meals, transfer the subject's therapy to insulin lispro on a unit-for-unit basis. Note: At the discretion of the investigator, it is permissible to reduce the total daily insulin lispro dose by up to 10%.

- If the subject's current regimen of bolus insulin is administered less than 3 times per day or more than 3 times per day, calculate the total daily bolus dose and divide it into 3 equal doses, administered with each of the 3 main meals. Alternatively, at the discretion of the investigator, if felt to be clinically preferable, it is permissible to allocate different starting doses of insulin lispro to each of the 3 main meals, maintaining the same total daily bolus dose. Note: As above, at the discretion of the investigator, it is permissible to reduce the total daily insulin lispro dose by up to 10%.

During the Standardization Period, insulin lispro may be adjusted to achieve glycemic targets as close to normal as possible without untoward hypoglycemia in accordance with product labeling in the respective country and standards of care at the study center. The treat-to-target titration algorithm for insulin glargine (Section 5.1.3.2, Table 3) is intended for use only during the Treatment Period.

Metformin

Subjects taking metformin as background antidiabetic medication will remain on their current dose for the duration of their participation in the study, unless a decline in kidney function results in a contraindication for metformin use. Metformin is to be stopped if the subject's eGFR, calculated according to the MDRD formula, decreases during the study to a level where metformin is contraindicated according to its label (as appropriate for each participating country).

5.1.2. Dosing Guidance During the Treatment Period

The dosing guidance for albiglutide, insulin lispro, insulin glargine, and metformin from Baseline/Randomization through the end of the Treatment Period is summarized in Table 2.

Table 2 Dosing Guidance for Albiglutide, Insulin Lispro, Insulin Glargine, and Metformin Treatment

Medication	Albiglutide + Insulin Glargine Group	Insulin Glargine + Insulin Lispro Group
Albiglutide	Baseline/Randomization: Start weekly SC injection at 30 mg. Week 4: Uptitrate to 50 mg weekly SC injection for the remainder of the Treatment Period.	None
Insulin lispro	Baseline/Randomization: Each insulin lispro dose will be downtitrated to half that used in the Standardization Period. ¹ Week 4: Stop insulin lispro for the remainder of the Treatment Period; insulin lispro may be re-introduced after Week 8 (See Section 5.1.3.5)	Baseline/Randomization: Continue at the same doses as at the end of the Standardization Period and adjust doses as per instructions in Section 5.1.3.2.
Insulin glargine	Continue at the same dose as at the end of the Standardization Period ¹ and adjust dose as per instructions in Section 5.1.3.2.	Continue at the same dose as at the end of the Standardization Period and adjust dose as per instructions in Section 5.1.3.2.

Medication	Albiglutide + Insulin Glargine Group	Insulin Glargine + Insulin Lispro Group
Metformin	Subjects will remain on their current dose for the duration of their participation in the study. ²	Subjects will remain on their current dose for the duration of their participation in the study. ²
Re-introduction of insulin lispro (if required)	After Week 8: See Section 5.1.3.5	Not applicable

SC = subcutaneous.

1. As described in Section 1.3.1, the risk of hypoglycemia is increased when albiglutide is used in combination with insulin; therefore, subjects may require a lower dose of insulin and should be monitored closely.
2. Unless a decline in kidney function results in a contraindication for metformin use. Metformin is to be stopped if the subject's estimated glomerular filtration rate, calculated according to the Modification of Diet in Renal Disease formula, decreases during the study to a level where metformin is contraindicated according to its label (as appropriate for each participating country).

5.1.3. Dose Titration During the Treatment Period

5.1.3.1. Albiglutide Titration

The albiglutide dose in this study will start at 30 mg weekly and be uptitrated at Week 4 to 50 mg weekly.

Albiglutide may be administered at any time of day without regard to meals. It should be administered once a week on the same day each week. The day of weekly administration can be changed if necessary as long as the last dose was administered 4 or more days previously. If a dose is missed, it should be administered as soon as possible within 3 days after the missed dose. Thereafter, subjects can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, subjects should wait and administer their next regularly scheduled weekly dose.

If a subject misses 2 or more consecutive doses, the investigator should contact the medical monitor, who will make a decision (on a case-by-case basis) on whether the subject should be withdrawn from the study for noncompliance.

Note: In this study, downtitration of albiglutide 50 mg weekly to 30 mg weekly is not permitted.

5.1.3.2. Insulin Titration

The intent of the American Diabetes Association and the European Association for the Study of Diabetes consensus statement for the treatment of T2DM is to maintain fasting and preprandial glucose values as close to a normal range as possible without untoward hypoglycemia or other adverse effects of treatment [Inzucchi, 2015; Inzucchi, 2012; Nathan, 2008; Nathan, 2006]. Less stringent HbA_{1c} goals are appropriate for other subjects, such as those with a history of severe hypoglycemia, limited life expectancy, advanced complications, or extensive comorbid conditions.

All subjects should measure their blood glucose values as detailed in Section 6.2.2.

NOTE: The use of a GLP-1R agonist (albiglutide) is expected to decrease the need for exogenous insulin. Therefore, the investigator will need to ensure careful

follow-up of each subject accordingly, particularly during the first few weeks of treatment, and reduce insulin doses if the subject experiences hypoglycemia or there is a significant risk of hypoglycemia.

Weekly telephone calls (if there is no scheduled study visit) must take place between the investigator and subject from the start of the Treatment Period through Week 16 and at Week 22, Week 25, and as required until the end of the Treatment Period, in order to optimize insulin titration (Table 6).

Insulin Glargine Titration

Both treatment groups will follow the same insulin glargine titration algorithm during the Treatment Period.

The main focus for the initial insulin titration should be on the basal insulin given before bedtime. Although optimization of insulin glargine should continue throughout the Treatment Period, it is expected that the basal insulin dose will have been stabilized for all subjects after about 6 weeks.

Prior to each study visit and telephone contact during the Treatment Period, a **recommended** dose of insulin glargine will be based on the mean of the subject's last 3 available before breakfast SMBG values (at least 2 of which are consecutive) and the titration algorithm for insulin glargine provided in Table 3. It is important that the investigator use his or her medical judgment in determining whether or not the algorithm **recommended** dose adjustment is appropriate for a particular subject at each time point. Of importance, decisions should be made taking into consideration all available information, such as symptoms of hypoglycemia or hyperglycemia, current total daily dose of insulin, and previous responses to dose adjustments, as well as additional glucose measurements (lowest of the last 3 SMBG values, other SMBG values in the week preceding the dose adjustment decision, or FPG [from a central laboratory]).

If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of SMBG measurements in this treat-to-target study.

Table 3 Titration Algorithm for Recommended Insulin Glargine Dose Adjustment

Before Breakfast Blood Glucose ¹		Adjustment of Insulin Glargine (IU) ²
mg/dL	mmol/L	
<56 ³	<3.1 ³	-4 For a dose >50 U, consider 10% dose reduction
56 – 69 ³	3.1 – 3.8 ³	-2 For a dose >50 U, consider 5% dose reduction
70 – 79	3.9 – 4.4	-1
80 – 109 = Target	4.5 – 6.0 = Target	No adjustment
110 – 139	6.1 – 7.7	+2
140 – 179	7.8 – 9.9	+4
≥180	≥10.0	+6
If severe hypoglycemia (requiring assistance) or any other clinically significant hypoglycemia (e.g., nocturnal hypoglycemia) was documented since the last dose adjustment		Decrease insulin dose 10% to 15%, at the investigator's discretion

1. Mean of measurements from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of self-monitored blood glucose measurements.
2. Modified based on the insulin titration algorithms in the BEGIN basal-bolus type 2 study [Garber, 2012] and other published treat-to-target studies [Rosenstock, 2008; Abrahamson, 2012; Mathieu, 2014; Riddle, 2014].
3. Investigator may defer adjustment if there is an obvious reason for the low value such as a missed meal.

Any insulin titration that differs from the algorithm recommended dose must be commented on by the investigator and the reason documented on the appropriate page of the eCRF. If adequate documentation is not provided in the eCRF, a protocol deviation will be recorded.

If the before breakfast glucose target has been achieved, but it is felt that the basal insulin needs further optimization, then alternatives (e.g., moving the basal injection to the morning or splitting the basal dose into twice daily injections) can be discussed with the medical monitor overseeing the titration and documented.

Insulin Lispro Titration

Insulin titration should start with insulin glargine given before bedtime. After about 6 weeks, it is expected that the basal insulin glargine dose will have been stabilized and the insulin lispro titration may begin.

Following randomization to study medication, insulin lispro will be titrated differently in each treatment group.

In the albiglutide plus insulin glargine group, the insulin lispro dose will be downtitrated at the Baseline/Randomization visit to half that used at the end of the Standardization Period. At Week 4, insulin lispro will be completely discontinued and should remain discontinued for the remainder of the Treatment Period; unless the subject meets the criteria for insulin lispro re-introduction (see Section 5.1.3.5).

In the insulin glargine plus insulin lispro treatment group, the dose adjustment of insulin lispro given in association with a meal is based on the blood glucose measurements taken prior to the subsequent meal. Therefore, blood glucose measurements taken Prior to Lunch are utilized to adjust the dose of insulin lispro taken with breakfast, the blood glucose measurements taken Prior to Dinner are utilized to adjust the dose of insulin lispro taken with lunch, and the blood glucose measurements taken Prior to Bedtime are utilized to adjust the dose of insulin lispro taken with dinner. Following Baseline/Randomization, the main focus for the initial insulin titration should be on the basal insulin before considering changes in the bolus insulin, unless the investigator finds it absolutely necessary to adjust the bolus insulin first.

Prior to each study visit and telephone contact during the Treatment Period, a **recommended** dose of insulin lispro for each specific meal will be based on the mean of the subject's last 3 available preprandial SMBG values (at least 2 of which are consecutive) and the titration algorithm for insulin lispro provided in Table 4. It is important that the investigator use his or her medical judgment in determining whether or not the algorithm **recommended** dose adjustment is appropriate for a particular subject at each time point. Of importance, decisions should be made taking into consideration all available information, such as symptoms of hypoglycemia or hyperglycemia, current total daily dose and distribution of insulin lispro doses, and previous responses to dose adjustments, as well as additional glucose measurements (lowest of the last 3 SMBG values, other SMBG values in the week preceding the dose adjustment decision, or FPG [from a central laboratory]) other than the mandatory ones.

If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact, unless in the investigator's judgment, a dose adjustment is warranted at that time. The subject should be retrained on the importance of SMBG measurements in this treat-to-target study.

Table 4 Titration Algorithm for Recommended Insulin Lispro Dose Adjustment

Prior to Lunch, Prior to Dinner, Prior to Bedtime Blood Glucose ¹		Adjustment of Lispro Insulin (U) ²
mg/dL	mmol/L	
≤99 without obvious explanation	≤5.5 without obvious explanation	-2 ³ For a dose >50 U, consider a 5% to 10% dose reduction at the discretion of the investigator
100 – 119 = Target	5.6 – 6.6 = Target	No adjustment
120 – 139	6.7 – 7.7	+2
140 – 179	7.8 – 9.9	+3
≥180	≥10.0	+4
If severe hypoglycemia (requiring assistance) or any other clinically significant hypoglycemia was documented since the last dose adjustment		Decrease insulin dose at the investigator's discretion (i.e., 10% to 15%)

1. Mean of measurements from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact, unless in the investigator's judgment, a dose adjustment is warranted at that time. The subject should be retrained on the importance of self-monitored blood glucose measurements (SMBG).
2. Modified based on the insulin titration algorithms in the BEGIN basal-bolus type 2 study [Garber, 2012] and other published treat-to-target studies [Rosenstock, 2008; Abrahamson, 2012; Mathieu, 2014; Riddle, 2014].
3. For subjects with an SMBG value less than 70 mg/dL without obvious explanation, insulin lispro may be stopped at the investigator's discretion.

Any insulin titration that differs from the algorithm recommended dose must be commented on by the investigator and the reason must be documented on the appropriate page of the eCRF. If adequate documentation is not provided in the eCRF, a protocol deviation will be recorded.

5.1.3.3. Intensive Subject Glycemic Surveillance and Management

In this treat-to-target study, which includes the discontinuation of prandial insulin in subjects randomly allocated to the albiglutide plus insulin glargine treatment arm as well as the intensification of basal-bolus insulin in subjects randomly allocated to the insulin glargine plus insulin lispro treatment arm, it is important that subjects receive adequate diabetic patient education and training and detailed clear explanations regarding all required study procedures related to glycemic management (see Section 6.2.4 and Section 6.2.5). It is also imperative that study investigators closely monitor available subject information and apply prompt medical judgment as necessary to maintain appropriate glycemic control.

To facilitate subject surveillance by the study investigator, the investigator will have access to information collected in the subject's e-diary, such as daily SMBG

measurements (see Section 6.2.2), daily insulin use (see Section 6.2.5), and subject-reported hypoglycemia (see Section 6.3.1). In addition, study investigators will receive notification of extreme SMBG measurements (i.e., SMBG measurements ≤ 50 mg/dL [≤ 2.8 mmol/L] and SMBG between 50 to 60 mg/dL [2.8 to 3.3 mmol/L]), as well as episodes of severe hypoglycemia recorded in the subject's e-diary. Additional details on these tools are provided in the accompanying SPM.

5.1.3.4. Documentation of Insulin Titration

Surveillance of insulin titration and documentation will be performed centrally. Within approximately 3 business days after a subject's study visit/telephone contact, the investigator must ensure that the following data are available for review by GSK/PPD:

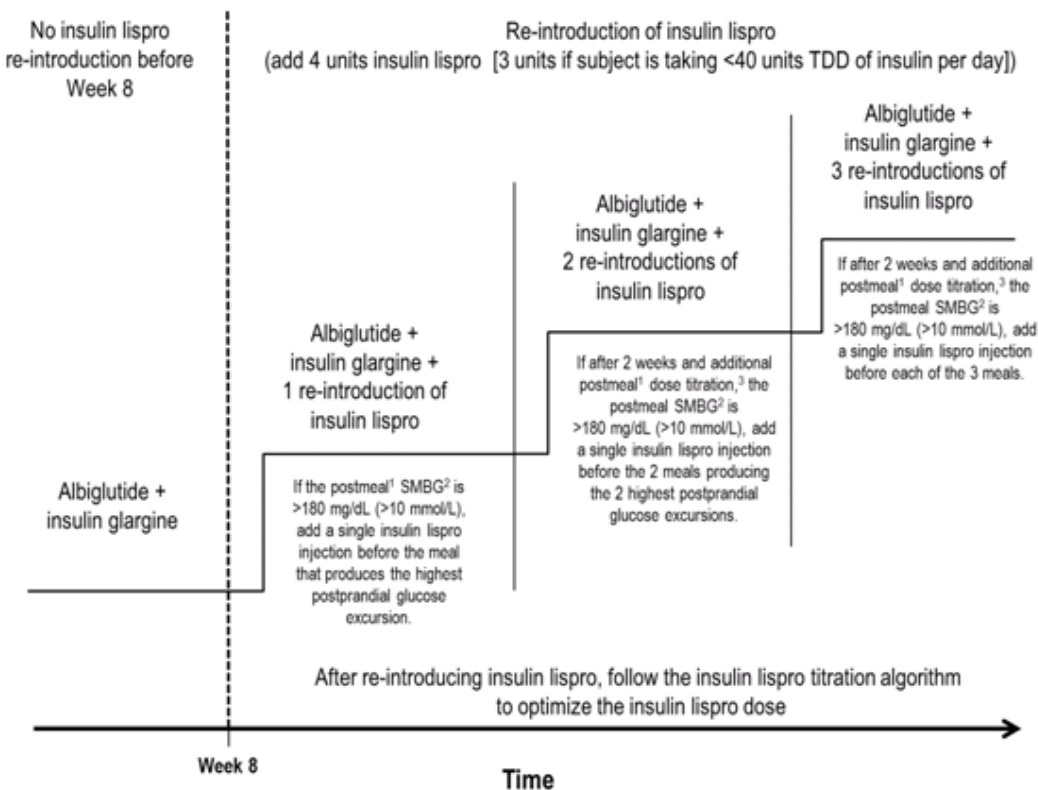
- Subject's SMBG values from the last 3 available days (at least 2 of which are consecutive) in the week before the study visit/telephone contact
- Insulin doses for 3 days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact
- Insulin doses recommended until the next study visit/telephone contact
- Comments on any deviation to the insulin titration algorithms must be entered into the eCRFs

The data regarding titration deviations will be reviewed by GSK/PPD. Based on this information, an inquiry as to why the investigator chose to deviate from the titration algorithm may be made, particularly when details of any SMBG readings, time, and date, or hypoglycemic symptoms used in such a decision are not provided or lack clarity. Not all deviations will lead to inquiry. When the investigator receives an inquiry, a response with the reasons for not adhering to the titration guideline should be sent to GSK/PPD within approximately 3 days. Depending on the response, additional inquiries may be sent.

5.1.3.5. Re-introduction of Insulin Lispro in the Albiglutide Treatment Group

Basal insulin plus once-weekly albiglutide may not provide adequate control of postprandial hyperglycemia in some subjects previously treated with basal-bolus insulin therapy. For subjects randomly assigned to treatment with albiglutide who continue to experience significant postprandial glucose excursions (i.e., >180 mg/dL [>10.0 mmol/L]), insulin lispro may be re-introduced after Week 8 (i.e., 4 weeks after discontinuation of insulin lispro and uptitration to albiglutide 50 mg). Re-introduction of insulin lispro will follow the standardized, stepwise approach as shown in [Figure 2](#).

Following the re-introduction of insulin lispro, subjects will remain in the study and continue to take insulin lispro in addition to randomly assigned once-weekly albiglutide and background insulin glargine. As determined by the investigator, subjects requiring re-introduction of insulin lispro may be seen more frequently by arranging unscheduled visits until their glycemic control has stabilized.

Figure 2 Re-introduction Algorithm for Insulin Lispro

HbA_{1c} = glycosylated hemoglobin. SMBG = self-monitored blood glucose.

Note: Figure modified with permissions (pending) from [Abrahamson 2012].

1. Post-breakfast (Prior to Lunch), post-lunch (Prior to Dinner), or post-dinner (i.e., Prior to Bedtime).
2. Mean of measurements from the last 3 available days (at least 2 of which are consecutive) in week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of SMBG measurements.
3. For insulin lispro dose titration, see Section 5.1.3.2, Table 4.

The algorithm in Figure 2 for re-introduction of insulin lispro should apply in the majority of circumstances; however, as the intent of glycemia management in subjects with T2DM is to individualize treatment goals to achieve a target HbA_{1c} level as close to normal as possible without significant hypoglycemia or other adverse effects of treatment, the investigator should use his/her judgment in determining benefit:risk of further insulin dose adjustment and modification, accordingly. In the event a subject experiences significant evidence of hyperglycemia (e.g., symptoms of polyuria and polydipsia and laboratory evidence of hyperglycemia) and the investigator determines that further dose adjustment with insulin is not in the best interest of the subject and that the subject requires rescue with another antidiabetic medication, the subject should be discontinued from the study and the appropriate rescue therapy initiated. Additionally, subjects not achieving a predefined threshold for glycemic control (confirmed persistent FPG ≥270 mg/dL [15.0 mmol/L]) at least 8 weeks after randomization may be considered

for study withdrawal based on the discretion of the investigator and the medical monitor (see Withdrawal Criteria in Section 4.5).

5.2. Treatment Assignment

Randomized treatment assignment will be done via the interactive voice response system (IVRS), and randomization will be implemented based on a sequestered fixed randomization schedule. Site personnel will call the IVRS to execute each randomization and initiate shipment of the investigational product once a subject has met all prerequisites for randomization and has completed all scheduled screening and standardization procedures.

Subjects will be assigned to study treatment in accordance with the randomization schedule. Eligible subjects will be stratified by screening HbA_{1c} value (<8.0% versus ≥8.0%), age (<65 years versus ≥65 years), and current use of background metformin (metformin use versus no metformin use).

Approximately 794 subjects will be randomly assigned to 1 of the following 2 open-label treatment groups in a 1:1 ratio such that

- Approximately 397 subjects are randomly assigned to albiglutide + insulin glargine (with or without metformin)
- Approximately 397 subjects are randomly assigned to intensification of insulin glargine + insulin lispro (with or without metformin)

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

5.3. Blinding

This will be an open-label study. An open-label study design was selected because insulin lispro is an injectable medication and thus double-blinding the study would require multiple dummy injections, which may not be in the best interest of the subject. Additionally, because insulin lispro will only be discontinued in the albiglutide treatment group, it is not feasible to blind the study. Furthermore, use of an objective laboratory endpoint will help mitigate bias that might otherwise be introduced if an open-label study design was not adopted.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when

applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

Accountability will be done for the investigational product (albiglutide) and other study treatments (insulin glargine and insulin lispro) at the time points specified in the Time and Events Table (Table 5). Subjects will be instructed to return all unused investigational product and used injector pens in order to perform drug accountability and determine compliance.

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

Subjects will be instructed to take their metformin as prescribed by their physician and will continue on this dose for the duration of their participation in the study unless there is a decline in kidney function (Section 5.1.1 and Table 2). Adherence to dosing instructions for metformin will be monitored for the duration of the study.

5.6. Concomitant Medications and Nondrug Therapies

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

5.6.1. Permitted Medications and Nondrug Therapies

Note: Albiglutide causes a delay of gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. During the albiglutide development program, drug interaction studies were conducted with digoxin, warfarin, oral contraceptives, and simvastatin, which demonstrated no clinically relevant pharmacokinetic (PK) or pharmacodynamic effects. Investigators should use clinical judgment and caution when prescribing concomitant medications.

The following concomitant medications are permitted:

- As-needed use of prescription and over-the-counter medications at the discretion of the investigator

Although stable doses of all concomitant medications are preferable, changes in medications during the study to appropriately treat clinical conditions that might arise, including worsening blood pressure control and dyslipidemia, are allowed.

Subjects will be monitored for renal function (eGFR calculated using the MDRD formula) during the study. Metformin and concomitant medications should always be

used within the label recommendations and stopped or adjusted according to the status of renal function and clinical conditions of the subject.

Investigators must adhere to the local labeling of the respective country (e.g., the summary of product characteristics in relevant European countries or the FDA-approved prescribing information) for all nonexcluded medications.

5.6.2. Prohibited Medications and Nondrug Therapies

Subjects must not use any of the following medications:

- Any antidiabetic medications (e.g., GLP-1R agonist, dipeptidyl peptidase-IV inhibitor, SU, thiazolidinedione, meglitinide, sodium-glucose transporter 2 inhibitor, or commercially available premixed basal and prandial insulin) other than the treatment they have been randomly assigned to, insulin glargine, insulin lispro, and their current regimen of background metformin, if applicable, being taken at Screening.
- Oral or systemically injected corticosteroids (inhaled, intra-articular, epidural, and topical corticosteroids are allowed); short courses of oral steroids (single dose or multiple doses for up to 7 days) may be permitted provided these cases are discussed with the medical monitor
- Antiretroviral drugs
- Prescription and over-the-counter weight loss drugs

If a subject receives a prohibited medication, a protocol deviation will be reported and continuation in the study will be discussed with and agreed upon by the medical monitor.

5.7. Treatment Between Week 26 (End of Treatment)/Early Withdrawal and After the Follow-up Visit

5.7.1. Treatment Between Week 26 (End of Treatment)/Early Withdrawal and Follow-up

After completion of the end-of-treatment (Week 26) or early withdrawal visits, subjects will return to the study center in 4 weeks for the Follow-up visit. During this time, subjects will continue insulin glargine or insulin glargine plus insulin lispro to maintain adequate glycemic control.

For subjects in the albiglutide plus insulin glargine treatment arm, the last dose of once-weekly albiglutide will occur at Week 25. As needed, insulin lispro may also be re-introduced during this period according to the re-introduction of insulin lispro algorithm provided in Section 5.1.3.5. Insulin glargine alone (in subjects for whom insulin lispro has not been re-introduced) or insulin glargine and insulin lispro (in subjects for whom insulin lispro has been re-introduced) can be adjusted to achieve or maintain glycemic targets as close to normal as possible without untoward hypoglycemia

in accordance with product labeling in the respective country and standards of care at the study center.

For subjects in the insulin glargine plus insulin lispro treatment arm, both insulin glargine and insulin lispro may be adjusted to achieve or maintain glycemic targets as close to normal as possible without untoward hypoglycemia in accordance with product labeling in the respective country and standards of care at the study center.

Note: During this time, subjects must not use any prohibited medications or nondrug therapies (see Section 5.6.2).

5.7.2. Treatment After the Follow-up Visit

No poststudy treatment will be provided by GSK.

After completion of the Week 26 visit, subjects will return to the study center in 4 weeks for the Follow-up visit and will complete the study. No poststudy treatment will be provided by GSK.

The investigator is responsible for ensuring that consideration has been given to the poststudy care of the subject's medical condition whether or not GSK is providing specific poststudy treatment.

Note: The half-life of albiglutide is approximately 5 days, and significant therapeutic concentrations can persist for 3 to 4 weeks after discontinuation. Therefore, the investigator should use caution when prescribing treatment after the withdrawal of active study medication, taking into consideration the long half-life of albiglutide. Thereafter, postwithdrawal treatments may be modified over time, as needed, at the investigator's discretion.

5.8. Treatment of Study Treatment Overdose

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

Excess insulin administration may cause hypoglycemia and hypokalemia. If an overdose of insulin glargine or insulin lispro occurs, the investigator should consult the approved product label for advice. Subjects should be monitored closely even after treatment of the acute event; recurrence should be managed appropriately.

6. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and times are presented in [Table 5](#). Telephone contact and times are presented in [Table 6](#). Study center visits through Week 16, inclusive, and all telephone contacts will have a visit window of ± 3 days; study center visits occurring after Week 16 will have a visit window of ± 7 days. Subjects will not be considered out of compliance if visit windows extend because of extraordinary events that make it impossible for subjects to complete a visit within the visit window (e.g., holidays, vacations, personal emergencies). However, determination of the maximum visit window deviation is at the discretion of the medical monitor.

Table 5 Time and Events Table – Study Visits

Study Procedure		Screening	Standardization		Treatment (For scheduled telephone calls, see Table 6)						Early Withdrawal Visit ¹	Follow-up Visit
					Baseline/ Randomization							
						Visit Week ²	1 -6 to -5	2 -4 ³	3 -1	4 0 ³		
Obtain written informed consent		x										
Obtain subject demography		x										
Obtain medical history		x										
Obtain disease history		x										
Obtain therapy history		x										
Review of inclusion/exclusion criteria		x	x	x	x							
Review of randomization criteria					x							
Efficacy Assessments												
Dispense home glucose monitoring device and e-diary			x									
Collect e-diary from subject												x
Provide advice on diet, exercise, home glucose monitoring, and hypoglycemia ⁵			x	x	x	x	x	x	x	x	x	x
Obtain 8-point SMBG profile ⁶					x			x		x		
Review glucose monitoring with subject ⁵				x	x	x	x	x	x	x	x	x
Administer diabetes questionnaires ⁷					x			x		x	x	
Obtain daily insulin dose information ⁸					x	x	x	x	x	x	x	
Safety Assessments												
Review concomitant medication		x	x	x	x	x	x	x	x	x	x	x
Perform physical examination ⁹		x			x			x		x	x	
Check visual acuity and funduscopy ¹⁰		x								x	x	
Obtain vital sign measurements ¹¹		x	x	x	x	x	x	x	x	x	x	x
Obtain body mass index information ¹¹		x										
Perform 12-lead ECG ¹²		x			x					x	x	
Assess for adverse events			x	x	x	x	x	x	x	x	x	x
Assess for serious adverse events		x	x	x	x	x	x	x	x	x	x	x
Assess for hypoglycemic events ¹³			x	x	x	x	x	x	x	x	x	x

Study Procedure		Screening	Standardization		Treatment (For scheduled telephone calls, see Table 6)						Early Withdrawal Visit ¹	Follow-up Visit
					Baseline/ Randomization							
	Visit	1	2	3	4	5	6	7	8	9		10
Week ²	-6 to -5	-4 ³	-1	0 ³	4	5 ³	10 ³	18 ³	26 ^{3,4}		30	
Laboratory Assessments												
Subject to fast overnight ¹⁴		x		x	x	x	x	x	x	x		
Obtain hematology sample ¹⁵		x			x			x		x	x	
Obtain chemistry sample ¹⁶		x		x ¹⁷	x	x ¹⁸	x ¹⁸	x	x ¹⁸	x	x	
Obtain urinalysis sample ¹⁹		x			x					x		
Obtain TSH sample ²⁰		x										
Obtain genetics sample ²¹					x							
Obtain urine pregnancy test ²²		x			x			x		x	x	
Obtain HBsAg and hepatitis C antibody ²³ samples		x										
Obtain HbA _{1c} sample		x ²⁴		x ²⁵	x	x	x	x	x	x		
Obtain fasting C-peptide sample ²⁶		x										
Obtain stimulated C-peptide sample 90 minutes after administration of a mixed-meal ²⁶		x										
Obtain lipid panel ²⁷		x			x			x		x		
Obtain biomarker sample					x					x		
Investigational product												
Dispense investigational product or insulin glargine and insulin lispro ²⁸			x	x	x	x		x	x	x		
Assess investigational product and other study treatment compliance					x	x		x	x	x	x	
Reduce or discontinue insulin lispro (albiglutide treatment group ONLY) ²⁹					x	x						
Albiglutide uptitration to 50 mg (albiglutide treatment group ONLY)						x						
Review the need for insulin glargine and/or insulin lispro adjustment ³⁰			x	x	x	x	x	x	x	x		
Register the subject's visit into the IVRS ³¹		x	x	x	x ³¹	x	x	x	x	x		

ECG = electrocardiogram; HbA_{1c} = glycosylated hemoglobin, HBsAg = hepatitis B surface antigen; IVRS = interactive voice response system; TSH = thyroid-stimulating hormone.

1. After completion of the early withdrawal assessments, subjects should return 4 weeks later for the Follow-up visit. In subjects who are withdrawn from the study due to an allergic or hypersensitivity reaction that is not reasonably attributed to another cause, a serum sample will be taken 8 weeks after stopping study medication for immunogenicity testing.
2. Study visits through Week 16, inclusive, will have a visit window of ± 3 days; study visits occurring after Week 16 will have a visit window of ± 7 days. Subjects will not be considered out of compliance if visit windows extend because of extraordinary events (e.g., holidays, vacations, personal emergencies). However, determination of the maximum visit window deviation will be at the discretion of the medical monitor.
3. Telephone calls to occur between study visits (if no study visit is scheduled, weekly from the start of the Standardization Period through Week 16, inclusive, and at Week 22, 25, and as required until the end of the Treatment Period [Table 6]) to advise subjects on insulin glargine and insulin lispro dose adjustments (see Section 5.1.1 and Section 5.1.3.2), adverse event monitoring, hypoglycemia monitoring, and concomitant medication usage.
4. The last dose of albiglutide is Week 25 for those subjects assigned to albiglutide + insulin glargine.
5. Standard diabetic dietary, exercise, and home blood glucose monitoring advice to be provided at Visit 2 (Week -4) and reinforced at each study site visit through the end-of-treatment visit. Subjects will monitor their glucose according to instructions. The investigator will review the glucose meter readings and adjust insulin glargine and insulin lispro doses in accordance with product labeling in the respective country and standard of care at the study center during the Standardization Period and per Table 3 and Table 4, respectively, during the Treatment Period. At each visit through the end-of-treatment visit (Visit 9; Week 26), subjects should be trained on the signs and symptoms of hypoglycemia, including nocturnal hypoglycemia, as well as the common causes of hypoglycemia. Subjects should also be educated on appropriate methods to help prevent hypoglycemia. It is also particularly important to advise subjects to contact the study site before any potential dietary change, as this may necessitate a change in insulin doses to avoid the development of hypoglycemia. Subjects should also be educated on how to treat hypoglycemia. For additional information, see Section 6.3.1.
6. An 8-point SMBG profile assessment (before and 2 hours after breakfast, lunch, and dinner; at bedtime; and at 2 AM): 3 times in the week prior to the Baseline/Randomization visit (Visit 4, Week 0), Visit 7 (Week 10), and Visit 9 (Week 26).
7. Treatment-related impact measure for diabetes (TRIM-Diabetes) and hypoglycemia fear survey-II (HFS-II) questionnaires to be administered prior to all other study assessments.
8. Daily insulin use to be recorded in the subject diary, at least 3 days preceding study visit/telephone contact at Week 1 through Week 16, inclusive, and at Week 18, 22, 25, and 26.
9. Perform complete physical examination at Screening and Week 26. Perform brief physical examination at other time points.
10. For the Screening assessment, a documented examination within six months of the Screening visit would also be acceptable but only when there was NO clinical change (e.g., decrease in visual acuity/visual field) since the last prior funduscopy. The end of treatment/early withdrawal assessment eye exam should be carried out by the investigator.
11. Height measured and body mass index calculated at Screening only. Weight, blood pressure, and heart rate (pulse); obtain blood pressure and pulse after sitting for at least 5 minutes.
12. All 12-lead ECGs to be performed before measurement of vital signs and collection of blood samples for laboratory testing. Subjects to be semirecumbent for 10 to 15 minutes before obtaining the ECG.
13. See Section 6.3.1 for hypoglycemic events criteria and reporting requirements. Subjects will be asked to report hypoglycemic events that occur between study visits in a diary.
14. Fasting is defined as no food or drink (except water) for at least 8 hours before blood draw.
15. Hematology to include complete blood count with red blood cell indices, white blood cell count differential, and platelet count.
16. Clinical chemistry to include glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, γ -glutamyltransferase, uric acid, magnesium, and phosphorus. Calculate estimated glomerular

filtration rate using the Modification of Diet in Renal Disease formula.

17. Fasting plasma glucose only.
18. Fasting plasma glucose, creatinine, alanine aminotransferase, total bilirubin, direct bilirubin, γ -glutamyltransferase, and alkaline phosphatase only.
19. Urinalysis to include specific gravity, pH, glucose, ketones, microalbumin, creatinine, blood, leukocyte esterase, and nitrites. (If warranted, a microscopic evaluation will be completed.)
20. Thyroid-stimulating hormone assessment at Screening only. Free T4 (reflex) will be measured if TSH is above upper limit of normal.
21. Blood sample for genetic research can be collected at any time during the study after the genetics informed consent has been obtained and the subject has been randomly assigned to treatment group.
22. Urine pregnancy test for women of childbearing potential only and at any time that pregnancy is suspected.
23. If hepatitis C antibody is positive, an RNA polymerase chain reaction should be performed on the same sample to confirm the result.
24. As described in Section 3.1, an optional fasting HbA_{1c} value may be determined using a Metrika kit or other finger-stick procedure to provide an initial guide of subject eligibility for investigators.
25. If the HbA_{1c} value at Week -1 is not $\geq 7.0\%$ and $\leq 9.0\%$, the assessment may be repeated on a weekly basis for a maximum of 2 additional weeks before randomization. The mean of all HbA_{1c} assessments (Week -1 plus the additional HbA_{1c} assessments) must be $\geq 7.0\%$ and $\leq 9.0\%$ for the subject to be eligible for randomization. Note: If a subject has confirmed (by a central laboratory) HbA_{1c} $< 7.0\%$ and $> 9.0\%$ at Week -1 or the subject decides not to continue repeat testing, he or she will be considered a standardization failure.
26. Subjects will have both fasting C-peptide and stimulated C-peptide testing. If the fasting C-peptide is < 0.8 ng/mL (< 0.26 nmol/L) but stimulated C-peptide 90 minutes after a standardized mixed meal is ≥ 1.5 ng/mL (≥ 0.5 nmol/L), the subject meets the C-peptide inclusion criterion.
27. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and free fatty acids.
28. Insulin glargine and insulin lispro will be dispensed during the Standardization Period at Visit 2 (Week -4) with additional dispensing at Visit 3 (Week -1) optional as needed to ensure adequate supply up to Visit 4 (Week 0). Dispense abiglutide, insulin glargine, and insulin lispro, as appropriate, according to randomization at Baseline/Randomization. See Section 5.7 for additional information regarding insulin usage after Week 26/Early Withdrawal.
29. For subjects randomly assigned to the abiglutide plus insulin glargine treatment group ONLY, reduce insulin lispro by 50% at Baseline/Randomization followed by complete (100%) discontinuation of insulin lispro at Week 4. No downtitration of insulin lispro occurs in the insulin glargine plus insulin lispro treatment group.
30. During the Standardization Period, adjust insulin glargine and insulin lispro, as required, in accordance with product labeling in the respective country and standard of care at the study center. During the Treatment Period, titrate insulin glargine and/or insulin lispro according to Table 3 and Table 4, respectively. Titration should be based on the mean of measurements from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of self-monitored blood glucose measurements.
31. Randomization to occur at the Baseline/Randomization visit.

Table 6 Time and Events Table – Telephone Calls

Study Procedure	Week	Standardization		Treatment Perform telephone contact with subject at the time points specified (±3 days) and as required for appropriate management of the subject															Follow-up
		-3	-2	1	2	3	6	7	8	9	11	12	13	14	15	16	22	25	28
Efficacy assessments																			
Review glucose monitoring with subject ¹		x	x ²	x	x	x	x	x	x	x ²	x	x	x	x	x	x	x	x ²	x
Review the need for dose titration ¹		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Obtain daily insulin dose information ³				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Safety assessments																			
Review of concomitant medication		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess for AEs/SAEs		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess for hypoglycemic events ⁴		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

AE = adverse event; SAE = serious adverse event.

1. During the Standardization Period, adjust insulin glargine and insulin lispro in accordance with product labeling in the respective country and standards of care at the study center. During the Treatment Period, titrate insulin glargine and/or insulin lispro according to [Table 3](#) and [Table 4](#), respectively. Titration should be based on the mean of measurements from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of SMBG measurements.
2. Remind subjects to perform 8-point SMBG profile assessment (before and 2 hours after breakfast, lunch, and dinner; at bedtime; and at 2 AM): 3 times in the week prior to the Baseline/Randomization visit (Visit 4, Week 0), Visit 7 (Week 10), and Visit 9 (Week 26).
3. Daily insulin use to be recorded in the subject diary, at least 3 days preceding study visit/telephone contact at Week 1 through Week 16, inclusive, and at Week 18, 22, 25, and 26.
4. See Section [6.3.1](#) for hypoglycemic events criteria and reporting requirements.

6.1. Critical Baseline Assessments

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

Critical baseline assessments will include: HbA_{1c}, body weight, FPG, and total daily dose of insulin (including insulin glargine and insulin lispro).

Cardiovascular medical history/risk factors will be assessed at Baseline/Randomization.

6.2. Efficacy

6.2.1. Efficacy Assessments

6.2.1.1. HbA_{1c} and FPG

Glycosylated hemoglobin and FPG will be measured at the time points specified in the Time and Events Table ([Table 5](#)).

6.2.1.2. Body Weight

Body weight will be measured at the time points specified in the Time and Events Table ([Table 5](#)). Body weight should be measured to the nearest 0.1 kg on a standard calibrated scale. Subjects should be dressed in light indoor clothes (no coat, jacket, etc.) without shoes and with a voided bladder. The same equipment should be used wherever possible.

6.2.2. Blood Glucose Monitoring

6.2.2.1. Home Blood Glucose Monitoring

All subjects in the study should be instructed to measure and record blood glucose values from their glucose meter a minimum of 4 times per day at the following times (except prior to Baseline/Randomization, Week 10, and Week 26 where an 8-point SMBG profile will be performed; see Section [6.2.2.2](#)):

- Before breakfast (at least 8 hours without food intake)
- Prior to Lunch
- Prior to Dinner
- At Bedtime

In addition, based on consultation with the investigator, the subject may be required on occasion to monitor at other time points (e.g., 2 hours after a meal or at approximately 3 AM) if such monitoring is deemed necessary and appropriate by the investigator.

All results of home blood glucose monitoring will be stored in the subject's glucose meter and communicated to the study site as directed by the investigator. The investigator will review the glucose meter readings at the study visit/telephone contact and adjust insulin glargine and insulin lispro doses. During the Standardization Period, insulin glargine and insulin lispro may be adjusted according to product labeling in the respective country and standard of care at the study center. During the Treatment Period, insulin glargine and/or insulin lispro will be adjusted per [Table 3](#) and [Table 4](#), respectively. Titration should be based on the mean of measurements from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of SMBG measurements. Additional glucose meter monitoring should be performed as per local practice. Surveillance of insulin titration will be performed as described in Section [5.1.3.3](#).

Weekly telephone calls (if there is no scheduled study visit) must take place between the investigator and subject from the start of the Standardization Period through Week 16 and at Week 22, Week 25, and as required until the end of the Treatment Period, in order to optimize insulin adjustments ([Table 6](#)).

NOTE: The use of a GLP-1R agonist (albiglutide) is expected to decrease the need for insulin and, therefore, the investigator will need to ensure careful follow-up of each subject accordingly.

6.2.2.2. 8-Point Self-Monitored Blood Glucose Profile

An 8-point glucose profile will be performed by the subject 3 times in the week prior to the Baseline/Randomization visit (Visit 4, Week 0), Visit 7 (Week 10), and Visit 9 (Week 26). Subjects should be instructed to measure and record blood glucose values using their glucose meter at the following times:

- Before breakfast (at least 8 hours without food intake)
- 2 hours post-breakfast
- Before lunch
- 2 hours post-lunch
- Before dinner
- 2 hours post-dinner
- At bedtime
- At 2 AM

6.2.3. Hypoglycemic Events

The incidence of severe and documented symptomatic hypoglycemic events through Week 26 will be evaluated as part of the efficacy assessments. Specific criteria for safety assessments related to monitoring hypoglycemic events are detailed in Section [6.3.1](#).

6.2.4. Diabetic Dietary, Exercise, and Home Blood Glucose Monitoring Advice

Standard diabetic dietary, exercise, and home blood glucose monitoring advice as well as on the signs and symptoms of hypoglycemia and on supplemental oral glucose treatment will be provided at Visit 2 (Week -2) and reinforced at each study site visit through the end-of-treatment visit (Week 26). In addition, subjects will be instructed to test their blood glucose any time they experience signs and symptoms of hypoglycemia to confirm that it is a hypoglycemic event (see Section [6.3.1](#)).

6.2.5. Daily Insulin Use

Subjects will record their daily insulin use in a diary. This information will be collected for at least 3 days before Baseline/Randomization and for at least 3 days preceding the study visit/telephone contact at Week 1 through Week 16, inclusive, and at Week 18, Week 22, Week 25, and Week 26. During each of these visits the investigator or designee will review the data recorded in the preceding 3 days, and if errors or gaps are identified (e.g., if the subject did not take insulin and had not entered “0 units,” the investigator will record the missing information from subject recall). Based on this information, mean daily insulin use over the 3 consecutive days (in units/kg body weight per day) will be calculated for each subject.

6.3. Safety

The following sections provide detail on the safety assessments. Planned time points for all safety assessments are listed in the Time and Events Tables ([Table 5](#) and [Table 6](#)). Unscheduled visits will occur as medically necessary. Detailed procedures for obtaining each assessment are provided in the SPM.

Liver chemistry stopping and follow-up criteria (including specific eCRF pages) and AEs are described in Section [6.3.6](#) and Section [6.3.7.1](#), respectively. The AEs of special interest are described in Section [6.3.9](#).

6.3.1. Hypoglycemic Events

Specific criteria for monitoring hypoglycemic events have been designed to ensure subject safety and to closely monitor hypoglycemia.

At each visit through the end-of-treatment visit (Visit 9; Week 26), subjects should be trained on the signs and symptoms of hypoglycemia (e.g., hunger, confusion, dizziness, anxiety, increased heart rate, visual disturbances), including nocturnal hypoglycemia (i.e.,

nightmares; night sweats; tired, irritable, or confused upon awakening), as well as the common causes of hypoglycemia. Subjects should also be educated on appropriate methods to help prevent hypoglycemia (i.e., strictly observe nutritional guidance from the physician or study site staff, consume small snacks before intense exercise, promptly communicate with the study site on “ill days” for additional guidance). It is also particularly important to advise subjects to contact the study site before any potential dietary change, as this may necessitate a change in insulin doses to avoid the development of hypoglycemia. Subjects should also be educated on how to treat hypoglycemia (e.g., oral glucose treatment with simple carbohydrates).

Subjects will be asked to report hypoglycemic events that occur between study visits using a diary. In this study, hypoglycemic events are defined according to recommendations by the American Diabetes Association and The Endocrine Society Workgroup on Hypoglycemia [Seaquist, 2013]. To aid correct classification and treatment of hypoglycemic events, subjects should be instructed to repeat SMBG measurements ≤ 70 mg/dL (≤ 3.9 mmol/L).

Severe Hypoglycemia

- Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration

Documented Symptomatic Hypoglycemia

- Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L)

Asymptomatic Hypoglycemia

- Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L)

Probable Symptomatic Hypoglycemia

- Probable symptomatic hypoglycemia is an event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L)

Pseudohypoglycemia

- Pseudohypoglycemia is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L) but approaching that level

Importantly, any report by a subject in the eDiary of a hypoglycemic event should be assessed and classified by the investigator per the above definitions, and recorded as a non-serious or serious adverse event if appropriate.

Any hypoglycemic event, regardless of intensity, that satisfies the definition of an SAE (Section 6.3.7.2) should be categorized as outlined in this section and reported appropriately in the SAE eCRF page.

6.3.2. Height and Vital Sign Measurements

Height will be measured and body mass index calculated at Screening only.

Assessment of vital signs (blood pressure and pulse rate) will be performed at every visit. During visits when ECGs are scheduled, vital sign measurements will be taken after the completion of the ECG sampling. Subjects may be either in a semirecumbent or seated position. During visits when ECGs are not scheduled, vital sign measurements will be taken while subjects are in a seated position after at least a 5-minute rest period. During visits where a blood draw is required, vital sign measurements will be taken prior to sample collection.

6.3.3. Electrocardiograms

A single 12-lead ECG recording (with subject in semirecumbent position for 10 to 15 minutes before obtaining the ECG) will be performed at the time points specified in the Time and Events Table (Table 5). All ECGs will be performed **before** measurement of vital signs and collection of blood samples for laboratory testing.

Investigators must compare the baseline ECG with the Visit 1 (Screening) ECG. Any changes indicative of a new MI or unstable cardiovascular condition (i.e., life-threatening arrhythmia) should prompt the investigator to **not administer the investigational product** but rather to evaluate and treat the subject per local standard of care. If subsequent evaluation reveals that a new MI has occurred or unstable/accelerated angina is documented, then the subject will be removed from the study (as they have met an exclusion criterion). If subsequent evaluation reveals no evidence of ischemic damage or instability, then study treatment may proceed. If any screening ECG demonstrates a possible old MI that was unknown to the investigator and the subject, the subject should be evaluated and treated, as appropriate.

6.3.4. Physical Examinations

Either a complete physical examination or brief physical examination will be performed at the time points specified in the Time and Events Table (Table 5). Subjects will have

visual acuity assessed at the screening and end-of-treatment (Week 26) visits as part of their physical examination. Visual acuity will be assessed using standard Snellen eye examination and funduscopy (dilation is preferred but not required).

The complete physical examination will include evaluation of the following organ or body systems:

- Skin (including injection site)
- Head, eyes, ears, nose, and throat
- Thyroid
- Respiratory system
- CV system
- Abdomen (liver, spleen)
- Lymph nodes
- Central nervous system
- Extremities

The brief physical examination will include evaluation of the following organ or body systems:

- Skin (including injection site)
- Respiratory system
- CV system
- Abdomen (liver, spleen)
- Central nervous system

6.3.5. Clinical Laboratory Testing

All protocol-required laboratory assessments, as defined in [Table 5](#), must be performed by the central laboratory, Quest Diagnostics Clinical Laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by Quest Diagnostics Clinical Laboratory. Reference ranges for all safety parameters will be provided to the site by Quest Diagnostics Clinical Laboratory.

If additional nonprotocol-specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), the results must be recorded in the subject's eCRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Hematology, clinical chemistry, urinalysis, and other laboratory assessments are detailed in the subsequent section and will be collected at time points specified in the Time and Events Table ([Table 5](#)).

Prior to the collection of blood samples, subjects should be fasting (no food or drink [except water] for at least 8 hours before sample collection). During visits when ECGs and vital sign measurements are scheduled, blood samples will be collected after the completion of these assessments.

Hematology:

- Complete blood count with red blood cell indices, white blood cell count differential, and platelet count

Clinical Chemistry:

- Glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase (ALP), ALT, aspartate aminotransferase (AST), γ -glutamyltransferase, uric acid, magnesium, and phosphorus

Urinalysis:

- Specific gravity, pH, glucose, ketones, microalbumin, creatinine, blood, leukocyte esterase, and nitrites (If warranted, a microscopic evaluation will be completed)

Other urine tests at time points specified in the Time and Events Table ([Table 5](#)):

- Urine pregnancy test (β -HCG) for female subjects of childbearing potential

Other blood tests at time points specified in the Time and Events Table ([Table 5](#)):

- HbA_{1c}
 - Note: As described in Section [3.1](#), an optional fasting HbA_{1c} value may be determined using a Metrika kit or other finger-stick procedure to provide an initial guide of subject eligibility for investigators.
- Fasting C-peptide and stimulated C-peptide 90 minutes after a standardized mixed meal
- TSH. If TSH is above the ULN, free T₄ (reflex) will also be measured
- Lipid panel: total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and free fatty acids
- Hepatitis B surface antigen
- Hepatitis C antibody. If hepatitis C antibody positive, an RNA polymerase chain reaction should be performed on the same sample to confirm the result

6.3.5.1. Estimated Glomerular Filtration Rate

In order to monitor kidney function, eGFR will be calculated using the MDRD formula [Levey, 2009] at time points specified in the Time and Events Table (Table 5), using the following formula:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{S}_{\text{Cr}})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}),$$

where S_{Cr} is serum creatinine.

6.3.6. Liver Chemistry Stopping and Follow-up Criteria

Phase III-IV liver chemistry stopping and follow-up criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Phase III-IV liver chemistry stopping criteria 1-5 are defined below and are presented in a figure in [Appendix 2](#):

1. ALT $\geq 3 \times \text{ULN}$ and bilirubin $\geq 2 \times \text{ULN}$ ($>35\%$ direct bilirubin) (or ALT $\geq 3 \times \text{ULN}$ and international normalized ratio [INR] >1.5 , if INR measured)

NOTE: If serum bilirubin fractionation is not immediately available, withdraw study medication for that subject if ALT $\geq 3 \times \text{ULN}$ and bilirubin $\geq 2 \times \text{ULN}$. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT $\geq 8 \times \text{ULN}$
3. ALT $\geq 5 \times \text{ULN}$ but $<8 \times \text{ULN}$ persists for ≥ 2 weeks
4. ALT $\geq 3 \times \text{ULN}$ if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia)
5. ALT $\geq 5 \times \text{ULN}$ but $<8 \times \text{ULN}$ and cannot be monitored weekly for ≥ 2 weeks

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** withdraw investigational product for that subject
- Report the event to GSK/PPD **within 24 hours** of learning its occurrence
- Complete the liver event eCRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT $\geq 3 \times \text{ULN}$ **and** bilirubin $\geq 2 \times \text{ULN}$ ($>35\%$ direct) (or ALT $\geq 3 \times \text{ULN}$ **and** INR >1.5 , if INR measured); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed “Hy’s Law,” **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).**

NOTE: If serum bilirubin fractionation is not immediately available, withdraw study medication for that subject if $ALT \geq 3 \times ULN$ **and** bilirubin $\geq 2 \times ULN$. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed
- Perform liver event follow-up assessments and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- Withdraw the subject from the study (unless further safety follow-up is required) after completion of the liver chemistry monitoring as described below
- Do not restart investigational product

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow-up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, ALP, and bilirubin) resolve, stabilize, or return to within baseline values

For criteria 2, 3, 4, and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24 to 72 hours** for repeat liver chemistries and liver event follow-up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, ALP, and bilirubin) resolve, stabilize, or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with $ALT \geq 5 \times ULN$ and $< 8 \times ULN$ that exhibit a decrease to $ALT \geq 3 \times ULN$, but $< 5 \times ULN$ and bilirubin $< 2 \times ULN$ without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the GSK/PPD medical monitor within 24 hours of learning of the abnormality to discuss subject safety
- Can continue investigational product
- Must return weekly for repeat liver chemistries (ALT, AST, ALP, and bilirubin) until they resolve, stabilize, or return to within baseline values
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above

- If, after 4 weeks of monitoring, ALT $<3 \times$ ULN and bilirubin $<2 \times$ ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values

For criteria 1-5, make every attempt to carry out the **liver event follow-up assessments** described below:

- Viral hepatitis serology including:
 - Hepatitis A immunoglobulin M (IgM) antibody
 - Hepatitis B surface antigen and hepatitis B core antibody (IgM)
 - Hepatitis C RNA
 - Cytomegalovirus IgM antibody
 - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
 - Hepatitis E IgM antibody
- Blood sample for PK analysis, obtained within 3 half-lives (15 days) of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw in the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase and lactate dehydrogenase
- Fractionate bilirubin, if total bilirubin $\geq 2 \times$ ULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia as relevant on the AE report form
- Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, or putative hepatotoxins, on the concomitant medications report form
- Record alcohol use on the liver event alcohol intake eCRF

The following are required for subjects with ALT $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN ($>35\%$ direct) but are optional for other abnormal liver chemistries:

- Antinuclear antibody, antismooth muscle antibody, and type 1 antiliver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct high-performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with

definite or likely acetaminophen use in the preceding week [[James](#), 2009]). **NOTE: not required in China.**

- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE:** If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction of hepatitis D RNA virus (where needed) [[Le Gal](#), 2005].
- Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease.

6.3.7. Adverse Events

The investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

6.3.7.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

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

6.3.7.2. Definition of an SAE

An SAE is any untoward medical occurrence that, at any dose:

- a. Results in death
- b. Is life-threatening

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

- c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

- d. Results in disability/incapacity, or

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

- e. Is a congenital anomaly/birth defect
- f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered

serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- g. All events of possible drug-induced liver injury with hyperbilirubinemia defined as $ALT \geq 3 \times ULN$ **and** bilirubin $\geq 2 \times ULN$ ($>35\%$ direct) (or $ALT \geq 3 \times ULN$ and $INR > 1.5$, if INR measured) termed “Hy’s Law” events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

NOTE: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin $\geq 2 \times ULN$, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.3.7.3. Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK/PPD medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired long QT syndrome
- Agranulocytosis/severe neutropenia
- Anaphylaxis and anaphylactoid reactions
- Hepatotoxicity
- Acute renal failure
- Seizure
- Stevens Johnson syndrome/toxic epidermal necrosis

6.3.8. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital sign measurements), including those that worsen from Baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject’s condition, are **not** to be reported as AEs or SAEs.

Liver chemistry stopping and follow-up criteria are described in Section 6.3.6.

6.3.9. Adverse Events of Special Interest

In the Phase IIIa clinical development program, AEs of special interest included several areas of safety-related concern for the T2DM population, particularly for a GLP-1R agonist such as albiglutide.

Specific eCRF pages will be used to capture additional details for the following AEs of special interest:

- Hypoglycemic events (Section 6.3.1)
- Liver events (Section 6.3.6)
- CV events (Section 6.3.9.1)
- Injection site reactions (Section 6.3.9.3)
- Potential systemic allergic reactions (Section 6.3.9.3)
- Pancreatitis (Section 6.3.9.4)
- Medullary thyroid cancer (Section 6.3.9.6)
- Diabetic retinopathy (Section 6.3.9.7)
- Pneumonia (Section 6.3.9.8)
- Atrial fibrillation/atrial flutter (Section 6.3.9.9)

The following additional AEs of special interest will be captured in the AE eCRF pages and analyzed as described in Section 8.3.5.2:

- GI events
- Pancreatic cancer (Section 6.3.9.5)
- Malignant neoplasms
- Appendicitis

6.3.9.1. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- MI/unstable angina
- Congestive heart failure
- Arrhythmias, including atrial fibrillation/flutter (see Section 6.3.9.9)
- Valvulopathy
- Pulmonary hypertension

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

This information should be recorded in the specific CV eCRF within 1 week of when the AE/SAE(s) are first reported.

6.3.9.2. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding CV (including sudden cardiac death) and non-CV death.

This information should be recorded in the specific death eCRF within 1 week of when the death is first reported.

6.3.9.3. Injection Site Reactions and Potential Systemic Allergic Reactions (e.g., Rashes, Urticaria, Angioedema, or Anaphylaxis)

Adverse events broadly evaluated as injection site reactions have been reported in subjects treated with albiglutide (refer to the IB for further information). Manifestations were generally mild to moderate and included localized rash, itching, redness, or pain in the area of the injection site. In some instances, reactions were noted to become more severe with subsequent injections. Injection site reactions should be reported as AEs or SAEs, as appropriate, and additional information on these events will be captured in specific eCRF pages.

Subjects should also be closely monitored for signs of potential allergic or drug hypersensitivity reactions including anaphylaxis, angioedema, generalized urticaria, rashes, dyspnea, or other potential manifestations of systemic allergic/immune reaction (e.g., glomerulopathy, vasculitides, and hematologic abnormalities). These events should be reported as AEs or SAEs based on the clinical evaluation of the subject. The reactions should be followed to completion as typical for any AE or SAE.

Subjects with allergic or drug hypersensitivity reactions that are not reasonably attributable to another cause should be withdrawn from the study and should **not** be rechallenged with albiglutide (see Section 4.5).

In the case of severe systemic allergic reactions that include anaphylaxis, angioedema, or other severe potential hypersensitivity reactions that cannot reasonably be attributed to another cause, five 1-mL serum samples should be obtained for immunogenicity testing (within 24 hours of the event if possible) and sent to the central laboratory (see details in the SPM) for immediate distribution to contracted testing facility for specific immunological testing (albiglutide-specific immunoglobulin E and other tests, as appropriate). A follow-up serum sample will be taken 8 weeks after final dose of study treatment in these subjects.

6.3.9.4. Pancreatitis

In clinical trials, acute pancreatitis has been reported in association with albiglutide and other GLP-1R agonists.

Subjects must be informed about the symptoms of pancreatitis in the subject information and instructed to contact the investigator immediately when they experience these symptoms. In the case of suspected pancreatitis, treatment with randomly assigned study medication should be withheld, and appropriate diagnostic measures initiated (clinical examination, laboratory parameters, diagnostic imaging). If the suspected pancreatitis is confirmed, the subject must be withdrawn from active treatment in the study.

Detailed information on suspected pancreatitis events will be collected in specific eCRF pages. Cases of suspected pancreatitis will be reviewed by an independent, blinded PAC (Section 9.8).

6.3.9.5. Pancreatic Cancer

Recently, the FDA and the EMA independently undertook comprehensive evaluations of a safety signal arising from postmarketing reports of pancreatitis and pancreatic cancer in patients using incretin-based drugs [Egan, 2014; EMA, 2013]. These investigations, included examination of data from a 2013 research report revealing a possible pancreatic safety signal [Butler, 2013]. They concluded that a causal relationship could not be established; however, they will continue to investigate as more data become available.

As a result, events of pancreatic cancer occurring during the study will be carefully evaluated in addition to careful evaluation of malignancies more broadly, given the interest in the potential for malignancies when GLP-1R agonists are used in combination with insulin [EMA, 2014].

6.3.9.6. Medullary Thyroid Cancer

Safety concerns regarding thyroid C-cell neoplasia were raised based on long-term rodent studies with GLP-1R agonists. If a thyroid nodule is detected at either Screening or during the study, this should be evaluated in view of the guidance documents that have recently been published in the United States and Europe [Cooper, 2009; Pacini, 2006]. For example, the American Thyroid Association Guidelines Taskforce and the European Thyroid Cancer Taskforce both recommend that the initial evaluation of a thyroid nodule detected by physical examination may include an ultrasound of the neck and fine-needle aspiration, as warranted. Additional examinations may also be required by the preliminary findings. If medullary thyroid cancer is diagnosed, study medication should be withdrawn. The results of any investigation should be recorded in specific eCRF pages.

6.3.9.7. Diabetic Retinopathy

In the Phase III program for albiglutide, the incidence of retinopathy events was similar between the albiglutide group and all comparators (see IB for further information).

However, there was a higher incidence of retinopathy events when albiglutide was compared with placebo (4.0% of subjects, event rate 2.17/100 person-years versus 2.1% of subjects, event rate 1.19/100 person-years, respectively). Additionally, there was a higher incidence in subjects receiving 50-mg albiglutide compared with 30-mg albiglutide (5.0% versus 2.1%, respectively). As such, GSK will continue to collect information on diabetic retinopathy events.

Detailed information on diabetic retinopathy will be collected in specific eCRF pages.

6.3.9.8. Pneumonia

In the Phase III program for albiglutide, there was a higher incidence of pneumonia events with albiglutide compared with other comparators (refer to the IB for further information) and as such, cases of pneumonia occurring during the study will be monitored.

Detailed information on pneumonia will be collected in specific eCRF pages.

6.3.9.9. Atrial Fibrillation/Atrial Flutter

In the Phase III program for albiglutide, there was a higher incidence of atrial fibrillation/atrial flutter events with albiglutide compared with other comparators. These events were more common in subjects who were male, older, or had renal impairment (refer to the IB for further information). Cases of atrial fibrillation or atrial flutter occurring during the study will be monitored.

Detailed information on atrial fibrillation and atrial flutter will be collected in specific eCRF pages.

6.3.10. Pregnancy

Any pregnancy that occurs during study participation (i.e., from Baseline/Randomization through the end of the Posttreatment Follow-up Period) must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK/PPD within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment must be promptly reported to GSK/PPD.

6.3.11. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

Adverse events will be collected from the start of the Standardization Period until the follow-up contact.

Serious AEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK/PPD within 24 hours, as indicated in Section [6.3.13](#).

6.3.12. Method of Detecting AEs and SAEs

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

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

6.3.13. Prompt Reporting of Serious Adverse Events and Other Events to GSK/PPD

Serious AEs, pregnancies, and liver function abnormalities meeting predefined criteria will be reported promptly by the investigator to GSK/PPD as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or death event	Initial and follow-up reports to be completed within 1 week of when the CV event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow-up reports to be completed within 1 week of when the CV event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Liver chemistry abnormalities				
ALT \geq 3 \times ULN and Bilirubin \geq 2 \times ULN (>35% direct) (or ALT \geq 3 \times ULN and INR>1.5, if INR measured) ¹	24 hours ²	"SAE" data collection tool. "Liver Event eCRF" and "Liver Imaging" and/or "Liver Biopsy" eCRFs, if applicable ³	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents ³
ALT \geq 8 \times ULN; ALT \geq 3 \times ULN with hepatitis or rash or \geq 3 \times ULN and <5 \times ULN that persists \geq 4 weeks	24 hours ²	"Liver Event" Documents (defined above) ³	24 hours	Updated "Liver Event" Documents ³
ALT \geq 5 \times ULN plus bilirubin <2 \times ULN	24 hours ²	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks ³	24 hours	Updated "Liver Event" Documents, if applicable ³
ALT \geq 5 \times ULN and bilirubin <2 \times ULN that persists \geq 2 weeks	24 hours ²	"Liver Event" Documents (defined above) ³	24 hours	Updated "Liver Event" Documents ³
ALT \geq 3 \times ULN and <5 \times ULN and bilirubin <2 \times ULN	24 hours ²	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks ³	24 hours	Updated "Liver Event" Documents, if applicable ³

ALT = alanine aminotransferase; CV = cardiovascular; eCRF = electronic case report form; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

1. An INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.
2. GSK/PPD must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., "Liver Event eCRF" and "Liver Imaging eCRF" and/or "Liver Biopsy eCRF," as applicable) should be completed as soon as possible.

For detailed descriptions of liver chemistry abnormalities, see Section 6.3.6.

The method of recording, evaluating, and following up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK/PPD are provided in the SPM. Procedures for poststudy AEs/SAEs are provided in the SPM.

6.3.13.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK/PPD is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK/PPD has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK/PPD will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK/PPD policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK/PPD will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.4. Health Outcomes

6.4.1. Health Outcome Assessments Not Included as Primary or Key Secondary Endpoints

6.4.1.1. TRIM-Diabetes Questionnaire

The TRIM-Diabetes questionnaire is a 28-item treatment satisfaction measure with 5 domains assessing treatment burden, daily life, diabetes management, compliance, and psychological health. Measures can be scored independently for each domain or as a total score. Higher scores indicate a better health state. The recall period is the past 2 weeks. The TRIM-Diabetes questionnaire is provided in [Appendix 3](#).

The TRIM-Diabetes questionnaire was developed according to the FDA patient-reported outcome guidance [[FDA Guidance for Industry, 2009](#)], and is based on the literature and significant input from patients with both type 1 diabetes mellitus and T2DM and from endocrinologists and internists. Its measurement properties were assessed in 2 studies and the tool demonstrated acceptable reliability, validity, and responsiveness [[Brod, 2009a](#); [Brod, 2009b](#); [Brod, 2011](#)]. Further work is needed to support a minimal important difference [[Brod, 2009b](#)].

The TRIM-Diabetes questionnaire will be administered in this study to assess treatment satisfaction within each treatment group of the study. The questionnaire will be administered to subjects using a paper format, at time points specified in the Time and Events Table ([Table 5](#)).

6.4.1.2. Hypoglycemia Fear Survey-II Questionnaire

The HFS-II questionnaire is a 33-item questionnaire with 2 subscales that measure: 1) behaviors to avoid hypoglycemia and its negative consequences and 2) worries about hypoglycemia and its negative consequences. This study will include the worry subscale only (18 items, score range 0 to 72). Responses use a 5-point Likert scale ranging from Never to Always. The HFS-II has a 6-month recall period. The HFS-II questionnaire is provided in [Appendix 4](#).

The HFS-II questionnaire was developed in response to the phenomenon of insulin-dependent diabetics whose fear of experiencing hypoglycemic episodes led them to purposely maintain elevated blood glucose levels [[Cox, 1987](#)]. The psychometric measurement properties of the tool have been assessed and found to be acceptable [[Irvine, 1994](#)].

The HFS-II questionnaire will be administered in this study to assess worries about hypoglycemia within each treatment group.

The questionnaire will be administered to subjects using a paper format, at time points specified in the schedule in the Time and Events Table ([Table 5](#)).

6.5. Genetics

Information regarding genetic research is included in [Appendix 1](#).

6.6. Novel Biomarkers

With the subject's consent, blood samples will be collected at Baseline/Randomization (Week 0) and at the end-of-treatment (Week 26) or early withdrawal visit (see Time and Events Table, [Table 5](#)) and may be used for the purposes of measuring novel biomarkers to identify factors that may influence T2DM and/or medically related conditions, as well as the biological and clinical responses to albiglutide. If relevant, this approach will be extended to include the identification of biomarkers associated with AEs. The timing of the collections may be adjusted on the basis of merging information in order to ensure optimal evaluation of the novel biomarkers.

Refusing to provide consent for the collection of these samples will not prevent the subject from participating in the rest of the study.

All samples will be retained for a maximum of 15 years after the last subject completes the trial.

6.7. Tracking of Albiglutide Pen Injector Failures and User Errors

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

NOTE: Pen injector failures and user errors associated with or result in events fulfilling the definition of an AE or SAE will follow the processes outlined in Section 6.3.7.

7. DATA MANAGEMENT

For this study, subject data will be entered via an eCRF into Oracle Clinical Remote Data Capture (OC RDC) system. Subject data will be available for viewing through access to the OC RDC system. Data provided from other sources will be received, reconciled, combined and transferred to GSK at predetermined time points.

Management of clinical data will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity and quality of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and a validated medication dictionary, GSKDrug.

The eCRFs (including queries and audit trails) will be sent at the end of the study in CD format to GSK to be retained. Each investigator will receive a copy of their site specific data in the same format to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

The primary hypothesis to be tested is that albiglutide plus insulin glargine (with or without metformin) will provide glycemic control (as measured by HbA_{1c} change from Baseline) noninferior to insulin lispro plus insulin glargine (with or without metformin) after 26 weeks of treatment in subjects with T2DM inadequately controlled on their current regimen of basal-bolus insulin therapy. If the null hypothesis of albiglutide inferiority is rejected, a test of superiority will be applied.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

Approximately 794 subjects will be randomly assigned in a 1:1 ratio to 2 treatment groups as described in Section 5.2. Eligible subjects will be stratified by screening HbA_{1c} value (<8.0% versus ≥8.0%), age (<65 years versus ≥65 years), and use of metformin (metformin use versus no metformin use). Assuming that 15% of subjects will be withdrawn early or will be lost to follow-up, approximately 337 subjects in each treatment group will complete 26 weeks of study assessments.

With 337 completed subjects in each of the 2 treatment groups, the study will have at least 90% power to reject the null hypothesis of inferiority for HbA_{1c} change from Baseline, assuming a noninferiority margin of 0.3%, an expected treatment group

difference of 0.0%, and a standard deviation of 1.2%, using a 2-sample, 1-sided t test with a testwise significance level of 0.025.

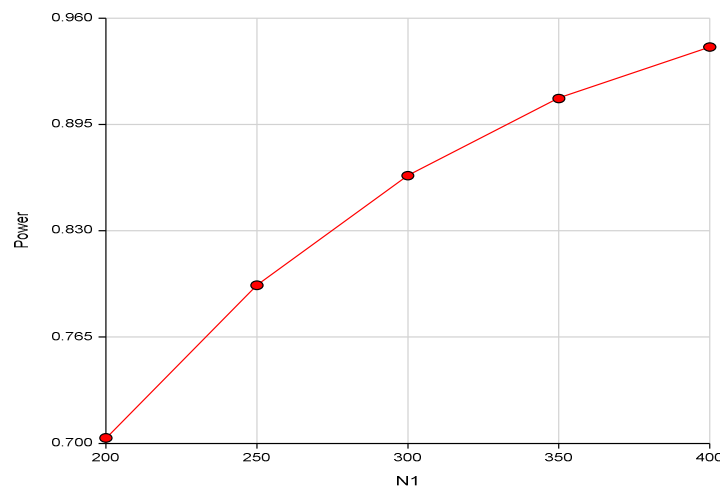
If noninferiority of albiglutide is established, superiority of albiglutide versus insulin lispro will be tested. Given the sample size of 337 completed subjects per treatment group and assuming a common standard deviation of 1.2, the minimum detectable difference in means between albiglutide and insulin lispro resulting in a significant test is 0.18, with a power of 50% and a type I error rate of 0.05.

The noninferiority margin of 0.30 was selected based on the expected effect of the active control. The assumed effect in terms of the within-treatment mean HbA_{1c} change from Baseline at Week 26 for the intensified basal-bolus insulin comparator (i.e., insulin glargine and insulin lispro) is at least 1.0% (M1 = 1.0%, as defined in Guidance for Industry Non-Inferiority Clinical Trials [FDA, 2010]). This assumption was based on data from subjects treated with insulin glargine and insulin lispro [Koivisto, 2011; Diamant, 2014; Garber, 2014]. The predefined margin of 0.30 that should be met in this trial preserves at least 70% of the assumed effect of the comparator (0.30 = 30% of M1 = M2, as defined in Guidance for Industry Non-Inferiority Clinical Trials) [FDA, 2010].

8.2.2. Sample Size Sensitivity

Figure 3 illustrates the power versus sample size (number of completed subjects per treatment group) to reject the null hypothesis of inferiority for HbA_{1c} change from Baseline, assuming a noninferiority margin of 0.3%, an expected treatment group difference of 0.0%, and a standard deviation of 1.2%, using a 2-sample, 1-sided t test with a testwise significance level of 0.025.

Figure 3 Power Versus Sample Size at the Noninferiority Margin of 0.3%



N1 = sample size.

8.2.3. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

The Full Analysis (FA) Population will include all subjects randomly assigned to treatment. Randomly assigned subjects who do not receive any study treatment will also be included. The subjects in the FA Population will be analyzed according to randomized treatment. The FA Population is the primary population for all efficacy analyses.

The Per-Protocol (PP) Population will include all FA subjects who complete study procedures through Week 26 or beyond and are compliant with the protocol. The subjects in the PP Population will be analyzed according to randomized treatment. The PP Population will be used for supportive analyses of key efficacy endpoints.

The Safety Population will include all subjects who receive at least 1 dose of randomized study medication. The subjects in the Safety Population will be analyzed according to the treatment received. The Safety Population will be used for all safety analyses.

Other analysis populations will be defined in the reporting and analysis plan (RAP).

8.3.2. Analysis Data Sets

Subjects withdrawn after not achieving a predefined threshold for glycemic control (confirmed FPG ≤ 270 mg/dL [15.0 mmol/L] at least 8 weeks after randomization) may be considered for study withdrawal. Subjects withdrawn for this reason will be considered to have completed the efficacy assessments for the primary analysis at the time of the assessment that triggers withdrawal.

Per the protocol, insulin lispro may be re-introduced after Week 8 for subjects in the albiglutide treatment group, following a standardized, stepwise approach. Efficacy and safety assessments after the re-introduction of lispro will be included in the statistical analysis as is, without special handling.

Clinical sites will be clustered by geographic region since the number of subjects per clinical site is expected to be rather small. Geographic regions will be defined based on geographic proximity, similarity of medical practice in diabetes, and number of subjects per region. Subjects per region will be constrained such that the region with the largest sample size is no more than 3 times that of the region with the smallest sample size. The clustering will be specifically defined in the RAP after clinical site selection and randomization are complete.

In general, the baseline value for each variable is defined as the last measurement collected prior to the first dose of randomized study medication.

Study day will be defined as the number of days from the first dose of randomized study medication. The date when a subject receives the first dose of randomized study medication is defined as Day 1. For events after the first dose date, study day is calculated as the difference in days between the first dose date and the date of interest, plus 1 day. For events that occur before the first dose date, study day is calculated as the difference in days between the first dose date and the date of interest. Thus, the day before first dose date is defined as Day -1.

In the conduct of the study, specific measures will be put in place to prevent and minimize missing data due to treatment withdrawals, noncompliance, etc. Upon study completion, the characteristics (frequency, causes) of the missing data, especially as related to the key efficacy endpoints, will be examined to inform the sensitivity analysis and imputation methods concerning missing data.

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

The primary endpoint is the change from Baseline in HbA_{1c} at Week 26. The primary analysis of the primary endpoint will be conducted using a mixed-effect model with repeated measures (MMRM) in the FA Population. The MMRM will only include nonmissing observations without imputation.

The model will include HbA_{1c} change from Baseline at all postbaseline visits as dependent variables; treatment, region, age category, current use of metformin, visit week, treatment-by-week interaction, and baseline HbA_{1c}-by-week interaction as fixed effects; baseline HbA_{1c} as a continuous covariate; and subject as a random effect. Treatment effects estimates (and associated hypothesis tests) of albiglutide will be evaluated within this MMRM model as least squares means contrasts relative to insulin lispro. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion.

The generalizability of the treatment effect will be evaluated within a supportive analysis of covariance (ANCOVA) model that adds terms for treatment-by-variable interaction. The variables to be interacted with treatment include baseline HbA_{1c}, region, age category, and current use of metformin. Absence of a significant treatment-by-variable qualitative interaction at the 0.10 level will be interpreted as supportive of the use of the main-effects model to evaluate the treatment efficacy hypotheses.

The primary endpoint will also be analyzed using the same MMRM model in the PP Population as supportive analysis.

Special attention will be paid to the handling of missing data in statistical analysis. The method for the primary analysis, MMRM, assumes missing at random. The sensitivity of the results of analysis to the method of handling missing values will be investigated, especially if the number of missing values is substantial or if the characteristics of missing values differ between treatment groups. Further details of the sensitivity analysis,

including imputation methods and assumptions about the missing data, are described in Section 8.3.5.1.

8.3.3.2. Other Comparisons of Interest

A key secondary endpoint is the proportion of subjects treated with once-weekly albiglutide that are able to replace prandial insulin without the need for re-introduction of insulin lispro. The 95% confidence interval of the sample proportion will be estimated, stratified by region, age category, and current use of metformin.

The proportion of subjects with hypoglycemia, as confirmed by plasma glucose monitoring <70 mg/dL (<3.9 mmol/L) and/or requiring third-party intervention through Week 26, will be compared between treatment groups, adjusting for baseline HbA_{1c} stratum, age group, current use of metformin, and region.

Other binary secondary endpoints, such as the proportion of subjects achieving HbA_{1c} treatment goals at Week 26 and the proportion of subjects achieving composite secondary endpoints (i.e., criteria involving HbA_{1c} target and hypoglycemia) will be analyzed analogous to the proportion of subjects with hypoglycemia.

Continuous secondary endpoints, e.g., changes over time in HbA_{1c}, FPG, and body weight, changes in daily insulin dose, changes in mean daily blood glucose based on 8-point SMBG, and changes in total number of weekly insulin injections will be summarized descriptively and analyzed using an MMRM (observed data). In the MMRM for non-HbA_{1c} endpoints, the corresponding baseline variable will be modeled as a covariate (in place of baseline HbA_{1c}) for variance reduction and to adjust for any baseline differences in treatment groups attributable to chance as well as the randomization stratification variables (HbA_{1c} stratum, age category, current use of metformin).

The number of hypoglycemic events with confirmed home blood glucose monitoring <70 mg/dL (<3.9 mmol/L) and/or requiring third-party intervention in 3-month intervals (i.e., from Baseline/Randomization to Week 12, >Week 12 to Week 26) will be compared between the treatment groups using a Poisson regression model with offset for the person-year, which will include treatment effect and covariates such as HbA_{1c} stratum, age (<65 years versus ≥ 65 years), current use of metformin (metformin use versus no metformin use), and region.

The time to meeting prespecified criteria for severe, persistent hyperglycemia at Week 26 will be analyzed for treatment group differences using pairwise log-rank tests within a Kaplan-Meier model.

A multiple comparisons adjustment strategy will be implemented for the multiple inferential tests among the primary endpoint and key secondary endpoints to preserve the study's nominal criterion significance level of 0.05. Further details will be specified in the RAP.

8.3.4. Interim Analysis

No interim analysis is planned for this study.

8.3.5. Key Elements of Analysis Plan

8.3.5.1. Efficacy Analyses

The primary analyses of the primary and secondary efficacy endpoints are described in Section 8.3.3. The details of any further planned analyses, including subgroup analysis and exploratory endpoints, will be provided in the RAP.

8.3.5.1.1. Impact of Missing Data on Primary Endpoint

Missing data are not explicitly imputed in the primary MMRM analysis; although, there is an underlying assumption that data are missing at random, including those withdrawn for lack of efficacy. All available scheduled postbaseline assessments up to endpoint are utilized and, via modelling of the within subject correlation structure, the derived treatment difference at Week 26 is adjusted to take into account missing data. The MMRM analysis (using saturated fixed effects and an unstructured variance-covariance matrix) is considered appropriate as the primary method of analysis, as it has been shown to give sensible answers to on-treatment questions in a range of practical situations [Siddiqui, 2009].

8.3.5.1.2. Extent of Missing Primary Analysis Data

Missing data is expected to arise mainly from subjects missing complete visits. The amount of missing data for those baseline covariates included in the statistical analysis is expected to be none or at worst minimal. If it should occur, that subject will effectively be lost to analysis. Missing data for HbA_{1c} between two nonmissing visits will be considered missing at random (intermediate missing data).

In this study, subjects who withdraw from treatment will be withdrawn from the study. In the eCRF, the reason for treatment discontinuation and the reason for withdrawal from the study are collected separately. Whenever the HbA_{1c} value at Week 26 is missing (end of the study), the reason can be determined based on available data in these two locations. The reason for missing data can be classified as follows: safety, procedural (including withdrawal of consent), or lack of efficacy.

8.3.5.1.3. Reasons for Withdrawal

Reasons for withdrawal are assumed to fall into three broad categories:

- Procedural (e.g., lost to follow-up, withdrew consent, protocol deviation, study closed/terminated, and investigator discretion): In this case, it is expected that an assumption of missing at random (MAR) is appropriate for imputation of HbA_{1c} data after withdrawal.

- Safety (e.g., AE, subject reached protocol-defined stopping criteria): It is expected that, in most cases, any change in safety related to these reasons for withdrawal would have been captured prior to the subject withdrawing from the study. In Study GLP108486 (albiglutide versus lispro over background glargine), 5% of subjects in the albiglutide group and <1% in the lispro group had AEs leading to withdrawal of active treatment through Week 26. In the albiglutide group, the most common AE leading to withdrawal was injection site reaction (1.1%). Missing HbA_{1c} values after withdrawal due to safety concerns will be considered to possibly be missing not at random (MNAR).
- Lack of efficacy: In this treat-to-target study, a substantial number of cases of withdrawal due to lack of efficacy is not expected. Missing HbA_{1c} values after withdrawal due to lack of efficacy are considered to possibly be MNAR.

Sensitivity analyses will be performed for data missing due to safety concerns or due to lack of efficacy.

8.3.5.1.4. Handling of Missing Data

The impact of missing data will be explored, as outlined below, for the Full Analysis Population only.

Examination of Missing Data Patterns

To examine the nature of missing data, cohorts of subjects will be defined based on the scheduled assessments (HbA_{1c} change from Baseline) that were completed at Weeks 4, 5, 10, 18, 26.

1. Subjects who have week 4 assessment only
2. Subjects who have assessments up to and including Week 5 only
3. Subjects who have assessments up to and including Week 10 only
4. Subjects who have assessments up to and including Week 18 only
5. Subjects who have assessments up to and including Week 26.

The number and percentage of subjects on each treatment in the 5 cohorts defined here will be tabulated. Graphical methods will be used to examine changes from Baseline over time to assess the pattern of outcomes prior to withdrawal.

Sensitivity Analyses – Multiple Imputation

Sensitivity analyses using multiple imputation methods will be conducted. Firstly, missing data between two nonmissing time points will be considered missing at random.

The following multiple imputation methods are proposed based on whether data are missing at random or not at random:

1. All missing data assumed MAR: Imputation is based on means and variances-covariances from subjects in the same treatment group as the withdrawn

subject and is comparable to MMRM. The main differences are that this approach uses separate covariance parameter estimation for each arm, and also separate regression parameters are estimated on baseline covariates within each arm. This more complex parameterization of the imputation model compared with the analysis model is valid. This approach will be used for all data missing post withdrawal. Here the estimand is one where after withdrawal all subjects progress in a similar way to those who remain in the trial. We expect the MMRM and this to give similar answers. If so, then it indicates any difference between the primary MMRM analysis and multiple imputation sensitivity analysis is due to the assumed effect modification and the assumed rates of HbA_{1c} increase after withdrawal, rather than anything to do with going from an MMRM approach to a multiple imputation approach.

2. Missing due to lack of efficacy or due to safety concerns using last mean carried forward (LMCF), that is MNAR: This approach assumes that a constant rate of increase in HbA_{1c} change from Baseline is experienced by subjects following withdrawal from the study for lack of efficacy or due to safety concerns. The MAR approach will be used for missing data due to procedural reasons. Sensitivity analyses using the LMCF approach will be performed using the following rates of HbA_{1c} increase: 0%/month, 0.1%/month, and 0.2%/month to explore the potential impact as in a tipping-point analysis. For each treatment group, these 3 rates will be assumed, resulting in 9 scenarios. The resulting treatment differences and associated P-values for noninferiority will be tabulated against the varying rates of HbA_{1c} increase. This estimand is one where those who withdraw for lack of efficacy or for safety concerns are assumed to revert to an unstable treatment regimen with an increasing rate of HbA_{1c}.

For each imputation data set, an analysis of variance will be carried using Week 26 data, both actual and imputed, using the same covariates as in the primary analysis. Contrasts of interest will be estimated and then combined across imputations using standard multiple imputation rules.

Additional scenarios for sensitivity analysis may be added and described in the RAP.

8.3.5.2. Safety Analyses

Subject demographics, medical history, prior and concomitant medications, study medication exposure, vital sign measurements, clinical laboratory values, 12-lead ECG readings, physical examination assessments, and AE rates will be summarized by treatment group using descriptive statistics. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. Some graphical summaries may be provided as well. No inferential testing will be performed on the safety variables.

For selected AEs of special interest, such as hypoglycemia, the exposure-adjusted incidence rate will also be calculated as the number of events in a given period divided by the total person time on treatment of subjects at risk within the same period. The exposure-adjusted incidence rate will be expressed as an annualized rate (expected number of events per 100 person-years).

Adverse events will be coded using MedDRA. Adverse events will be summarized in various subsets, including treatment-emergent AEs, related AEs, AEs leading to treatment discontinuation or withdrawal from study, SAEs, fatal AEs, etc. Adverse events will also be summarized by maximum intensity (mild, moderate, and severe).

Treatment-emergent AEs will be defined as any AEs, regardless of relationship to the investigational product, that occur after the first dose of the randomized study medication. Treatment-emergent AEs will also be further defined as on-therapy or post-therapy AEs for summary purposes.

Treatment-related AEs will be defined as any AEs that are considered by the investigator to be possibly, probably, or definitely related to the investigational product. In addition, if relationship information is missing, the AE will be considered treatment related.

Adverse events of special interest will also be summarized.

The number and percentage of subjects reporting specific events, such as specific GI events and injection site reactions, at each study week will be summarized and plotted over time. Characteristics of specific events, such as time to first occurrence, occurrence relative to preceding dose, and duration, will be summarized.

Hypoglycemic events will be analyzed separately from other AEs. All hypoglycemic events will be classified as severe, documented symptomatic, asymptomatic, probable symptomatic, and pseudohypoglycemia, as defined in Section 6.3.1.

Incidence (in total and by each category) of hypoglycemia, daytime hypoglycemia, and nocturnal hypoglycemia will be determined. Daytime hypoglycemia is defined as hypoglycemic events with an onset between 06:00 hours and 00:00 hours (inclusive). Nocturnal hypoglycemia is defined as hypoglycemic events with an onset between 00:01 hour and 05:59 hours (inclusive). The incidence of hypoglycemia with blood glucose <56 mg/dL (<3.1 mmol/L), regardless of symptoms, will also be determined.

Estimated GFR will be calculated using the MDRD formula and summarized descriptively.

8.3.5.3. Health Outcomes Analyses

Details for analyzing the data from the TRIM-Diabetes questionnaires and the HFS-II worry subscale will be provided in the RAP.

8.3.5.4. Genetic Analyses

See [Appendix 1](#) for details about the genetics analysis plan.

8.3.5.5. Novel Biomarker(s) Analyses

After completion of the clinical trial, if biomarker investigations are performed on samples collected during the study, the results will be reported separately from the main

clinical study report. Any endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki (based on the initial version accepted in 1996), including, but not limited to:

- IRB/IEC review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK/PPD will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., genetics assessments described in [Appendix 1](#), unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

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

GSK/PPD will monitor the study to ensure that the:

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

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

9.4. Quality Assurance

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

9.5. Study and Site Closure

The end of the study is when the last subject completes the Final follow-up visit (Week 30).

Upon completion or termination of the study, the GSK/PPD monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK/PPD standard operating procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK/PPD will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK/PPD will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK/PPD will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. GSK/PPD will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK/PPD audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK/PPD will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK/PPD standard operating procedures, and/or institutional requirements.

The investigator must notify GSK/PPD of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

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

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

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

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

The results summary will be posted to the Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit. When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

9.8. Pancreatitis Adjudication Committee

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

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11. APPENDICES

11.1. Appendix 1 - Genetic Research

Genetic Research Objectives and Analyses

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

- Response to medicine, including albiglutide, basal insulins, bolus insulins (prandial or rapid-acting insulins), or any concomitant medicines;
- T2DM susceptibility, severity, and progression and related conditions

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

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

Study Population

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

Study Assessments and Procedures

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

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

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

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

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

Informed Consent

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

Subject Withdrawal from Study

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

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

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

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

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

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to

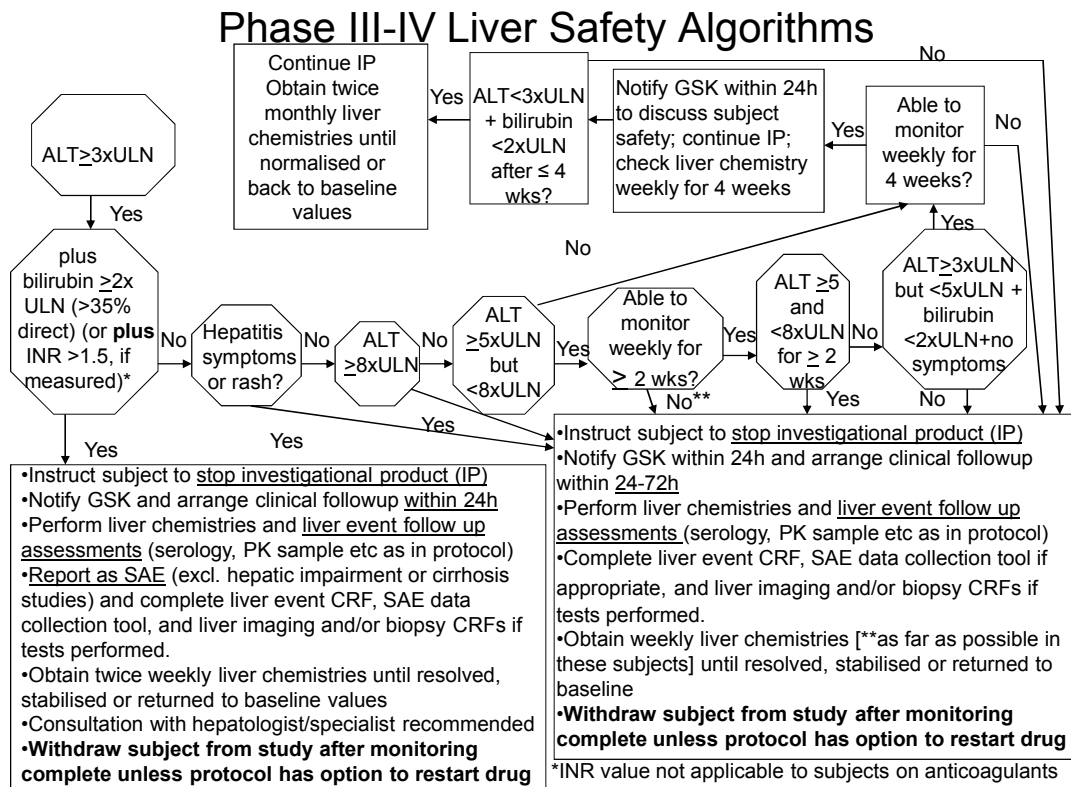
complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

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

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

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

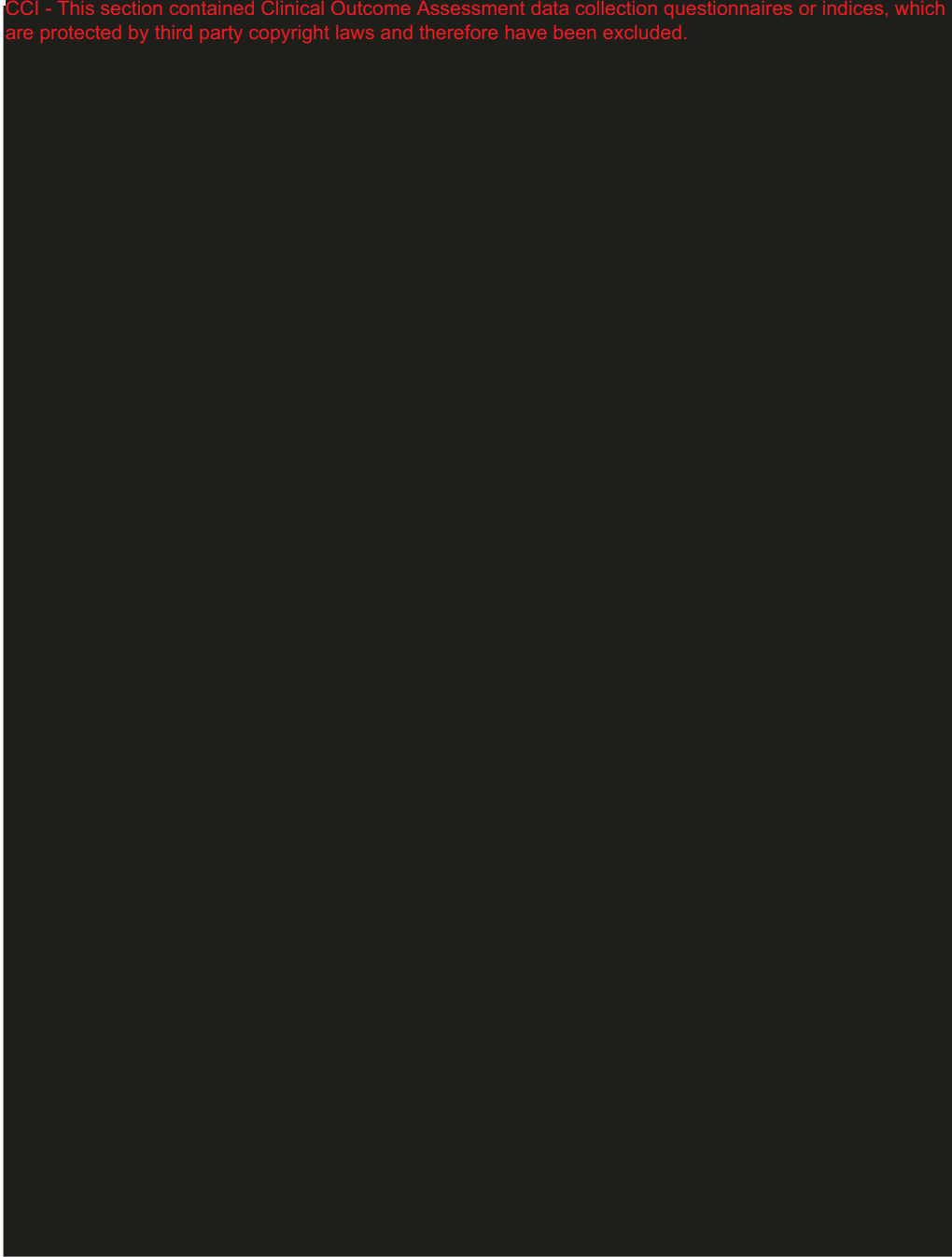
11.2. Appendix 2: Liver Chemistry Stopping and Follow-up Criteria



ALT = alanine aminotransferase; CRF = case report form; GSK = GlaxoSmithKline; INR = international normalized ratio; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal.

11.3. Appendix 3: Treatment-Related Impact Measure – Diabetes Questionnaire

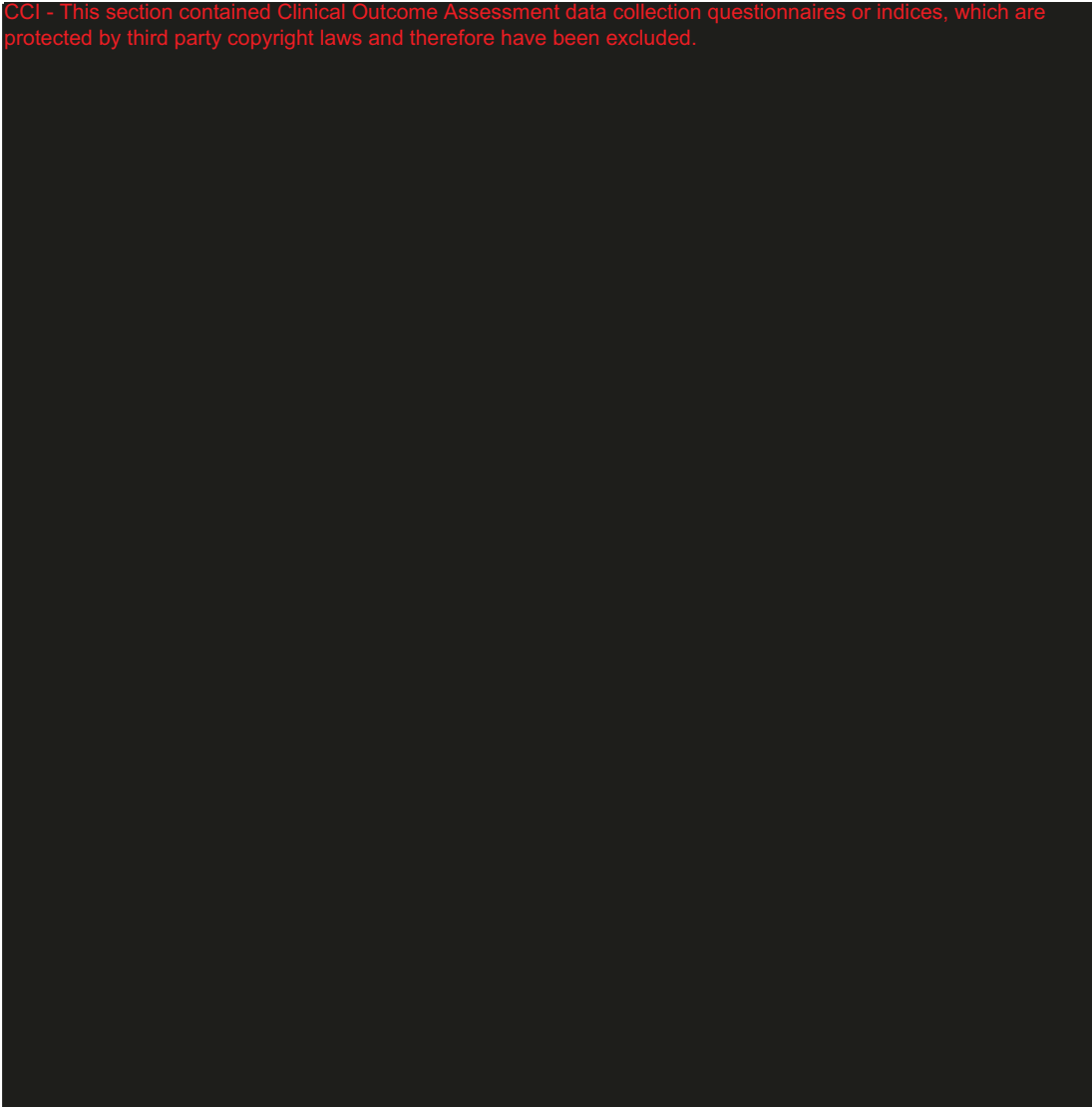
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



PPD

11.4. **Appendix 4: Hypoglycemia Fear Survey-II Questionnaire, Worry Subscale**

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



11.5. Appendix 5: Country-Specific Requirements

11.5.1. German-Specific Eligibility Requirements

Select eligibility criteria are specific to subjects participating at sites in Germany.

Section 4.2 includes German-specific text for inclusion #7 (bullet 2) stipulating that progestogen-only pills are only acceptable if they have a Pearl Index of less than 1.0 (e.g., those containing 75 µg desogestrel)

Section 4.3 includes German-specific text for exclusion #21 and #22 stipulating subjects are not eligible for study participation if they have been put in an institution because of official or legal order, or if they are employees (or the employee's relatives) of the sponsor, the contract research organization, or the investigative site, including the investigator or other site staff.

11.5.2. French Administrative Considerations and Specific Requirements

This appendix includes all the requirements of the French law (n° 2004-806 of 9th August 2004), and identifies, item per item, the mandatory modifications or additional information to the study protocol and includes specifics GSK requirements.

1. Concerning the “STUDY POPULATION”

- In line with the local regulatory requirements, the following text in section “**OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS**” (Section 4.4) is added :

A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category.

It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

~~~~~

#### 2. Concerning the “DATA ANALYSIS AND STATISTICAL CONSIDERATIONS” and specially in the “SAMPLE SIZE ASSUMPTION” (Section 8.2.1)

The expected number of patients to be recruited in France is declared to the French regulatory authority.

~~~~~

3. Concerning the “STUDY CONDUCT CONSIDERATIONS”

- In section “**Regulatory and Ethical Considerations, Including the Informed Consent Process**” (Section 9.2)

⇒ Concerning **the process for informing the patient** or his/her legally authorized representative, the following text is added :

French Patient Informed Consent form is a document which summarizes the main features of the study and allows collection of the patient's written consent in duplicate. It also contains a reference to the authorisation of Agence nationale de sécurité du médicament et des produits de santé (ANSM), the French National Agency for Medicines and Health Products Safety) and the approval from the French Ethic committee.

~~~~~

- In section concerning the “**NOTIFICATION TO THE HOSPITAL DIRECTOR**” (Section 9.2) the following text is added:

In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

~~~~~

- In section concerning the “**INFORMATION TO THE HOSPITAL PHARMACIST**” (Section 9.2) the following text is added:

In accordance with Article R.1123-64 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the IB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

~~~~~

- In section “**DATA MANAGEMENT**” (Section 7) the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GlaxoSmithKline Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act



n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through GlaxoSmithKline Laboratory (Clinical Operations Department).

~~~~~

4. Monitoring Visits (Section 9.3)

The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant (CRA) of GLAXOSMITHKLINE or of a service provider designated by GLAXOSMITHKLINE. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GLAXOSMITHKLINE or from a service provider designated by GLAXOSMITHKLINE. In addition, the Health Institution and the Investigator agree that the CRA or the service provider designated by GLAXOSMITHKLINE have direct access to all the data concerning the Study (test results, medical record, etc.). This consultation of the information by GLAXOSMITHKLINE is required to validate the data registered in the electronic Case Report Form (eCRF), in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

~~~~~

#### **5. Data entry into the eCRF (Section 7)**

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's eCRF use here below:

The Health Institution and the Investigator undertake:

- 1) That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the eCRF of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.
- 2) That the Investigator and the staff of the investigator center use the information technology (IT) Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
- 3) That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.

- 4) To keep the IT Equipment and/or access codes in a safe and secure place and to only authorize the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.
- 5) That the Investigator and the staff of the investigator center enter the data of the eCRF related to a patient visit in the 3 days following the date of the patient visit or, for the patient test results, in the 3 days following the reception of the results of such tests.
- 6) That the Investigator resolves and returns to GLAXOSMITHKLINE the data queries issued by GLAXOSMITHKLINE or a service provider designated by GLAXOSMITHKLINE within 7 days after the reception of the request of clarification or in a period of one (1) day during the final stage of clarification of the data base or in such other period as provided by GLAXOSMITHKLINE and/or a company designated by GLAXOSMITHKLINE.
- 7) To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
- 8) To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

~~~~~

6. CTR Publication (Section 9.7)

It is expressly specified that GLAXOSMITHKLINE and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GLAXOSMITHKLINE GROUP named Clinical Trial Registry (CTR) including the registration of all the clinical trials conduct by the GLAXOSMITHKLINE Group and this before or after the publication of such results by any other process.

7. Data Protection French Law of 6 January 1987 (CNIL) (Section 9.7)

In accordance with the Data Protection French Law of 6 January 1978 as modified, computer files used by GLAXOSMITHKLINE to monitor and follow the implementation and the progress of the Study are declared with the Commission nationale de l'informatique et des Libertés (CNIL) by GLAXOSMITHKLINE. The Investigator has regarding the processing data related to him a right of access, of rectification and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GLAXOSMITHKLINE

Group in France, Britain or United States, what the Investigator agrees by the signature of the present Protocol.

~~~~~

## 11.6. Appendix 6: Protocol Changes

### Protocol Amendment Number 01

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

- Inclusion criterion 1 was updated to limit the upper age range to 75 years of age (inclusive at the time of Screening).
- Inclusion criterion 2 was updated to increase the upper limit of the HbA<sub>1c</sub> value at Screening from 9.0% to 9.5%. In addition, an upper limit of 9.0% for the HbA<sub>1c</sub> value at Week -1 (pertaining to the additional inclusion criteria for randomization) was added. The rationale for these changes was to facilitate enrollment into the Screening Period while still allowing only subjects with an HbA<sub>1c</sub> value between 7.0% and 9.0%, inclusive, to be randomly assigned to study treatment.
- Inclusion criterion 4 was updated to indicate that the simulated C-peptide value (added at Screening) may be used for the qualification of subjects who do not meet the fasting C-peptide value but who meet all other eligibility criteria. The rationale for this addition to the inclusion criterion was to better characterize and exclude insulin-deficient T2DM subjects from participating in this clinical study where prandial insulin will be withdrawn from subjects randomly allocated to albiglutide. In subjects treated with exogenous insulin,  $\beta$ -cell stimulation in the fasting state may be reduced by the hypoglycemic effect of concomitant insulin administration [Jones, 2013; Maldonado, 2005].
- Inclusion criterion 9 was updated to include a statement to indicate that informed consent would be provided after consultation with the investigator. The rationale for this change was to clarify that subjects would be given the opportunity to ask all of their questions and fully understand the study before providing consent to participate.
- Inclusion criterion 10 was added to ensure that subjects enrolled in the study are suitable to participate in this treat-to-target study design, which includes intensified basal-bolus insulin therapy utilizing prespecified glycemic targets.
- The withdrawal criteria were updated to clarify which obligatory reasons require a subject to be withdrawn from the study.
- An additional phone call was added at Week 28. The rationale for this change was to monitor and adjust insulin glargine and insulin lispro doses between the Week 26/Early Withdrawal and Follow-up visit.
- The titration algorithms for insulin glargine (Table 3) and insulin lispro (Table 4) were updated. The rationale for these changes was to simplify the instructions,

modify the increments for dose adjustments, and to provide additional dose reductions at the investigator's discretion.

- Included additional information regarding subject education and training on the signs and symptoms, common causes, and self-management of hypoglycemia. The rationale for these additions was to enhance the language in the original protocol to reinforce the importance of education and training.
- Added an optional fasting HbA<sub>1c</sub> test at Screening using a Metrika kit or other finger-stick procedure to aid investigators in the selection of subjects who may be good candidates for the study.
- Figure 2 was updated to change the less than symbol to a greater than symbol in two places. The rationale for this change was that this was an error previously identified and addressed in a Note to File.
- Additional sensitivity analyses to assess the impact of missing data for the noninferiority test have been described. The rationale for this addition was based on the explicit request of a Regulatory Agency.
- Incorporated other administrative changes; the rationale for these changes is to ensure a clear and complete protocol for use at the study centers

### Specific Changes in the Text

#### Title Page:

Authors: PPD

#### Synopsis, Study Design:

- Subjects ~~with inadequate failing to achieve adequate~~ glycemic control (glycosylated hemoglobin [HbA<sub>1c</sub>]  $\geq 7.0\%$  and  $\leq 9.05\%$  at Screening) on their current basal-bolus insulin regimen (with ~~and or~~ without metformin) despite at least 3 months of treatment will be recruited into the study. **Subjects who achieve an HbA<sub>1c</sub> value  $\geq 7.0\%$  and  $\leq 9.0\%$  following the Standardization Period will be randomized into the study.**

**Table 1, Risk Assessment for Albiglutide (GSK716155)**

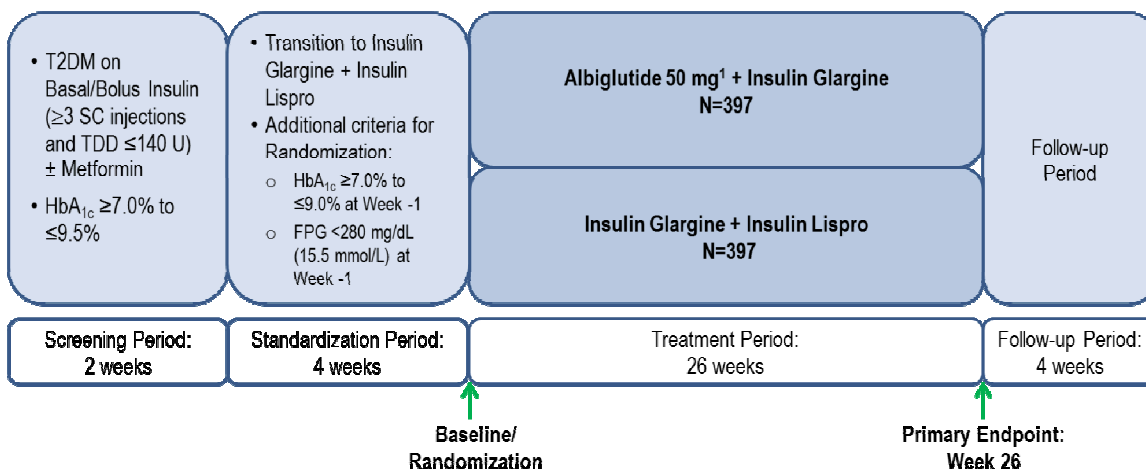
Risk of Clinical Significance: Insulin glargine and insulin lispro, Mitigation Strategy:

Subject education on the signs and symptoms of hypoglycemia (including nocturnal hypoglycemia), common causes of hypoglycemia, appropriate methods to help prevent hypoglycemia, and on the self treatment of hypoglycemic episodes (see Section 6.3.1)

Close monitoring for hypoglycemia and need for intervention (e.g., insulin dose adjustment, withdrawal from study participation) via frequent contact with subjects, who will self monitor blood glucose (see Section 4.5, and Section 5.1.3.3, and Section 6.2.2)

Risk communication via guidance for investigators (IB Section 6) and informed consent form for subjects

### Section 3.1, Study Design

**Figure 1, Study Design**

During the Screening Period (Week -6 through Week -5), subjects will provide written informed consent and undergo procedures to determine eligibility for study participation.

**Note: A fasting  $HbA_{1c}$  value may be determined using a Metrika kit (Metrika, Inc, Sunnyvale, California) or other finger-stick procedure to provide an initial guide of subject eligibility for investigators. The test is not required. The  $HbA_{1c}$  value obtained at this screening visit is to be used as a guide for the investigator. If the investigator feels that a subject is a good candidate for the study, the subject should continue with the screening visit and have  $HbA_{1c}$  assessed through the central laboratory. The central laboratory measure will serve as the official  $HbA_{1c}$  value to determine subject eligibility for entry into the Standardization Phase.**

### Section 3.2.5, Insulin Doses

The starting dose for basal insulin (insulin glargine) in the Standardization Period ~~will~~ **should** be the same (or 20% lower if the subject enters the study on 2 doses of basal insulin), on a unit-for-unit basis, as that taken by the subject during Screening; **see Section 5.1.1 for additional details.**

The starting dose for bolus insulin (insulin lispro) in the Standardization Period ~~will~~ **should** be the same, on a unit-for-unit basis, as that taken by the subject during Screening; **see Section 5.1.1 for additional details and guidance regarding permitted changes at the discretion of the investigator.**

During the Treatment Period, the study will allow individualization of the insulin dose in both treatment groups (i.e., insulin glargine in the albiglutide treatment group and both insulin glargine and insulin lispro in the basal bolus treatment group), with a treat-to-target approach and a titration regimen based on **SMBG values and other important information, such as hypoglycemia FPG and/or postprandial glucose values** (Table 3 and Table 4).

#### Inclusion Criterion 1:

Male or female, 18 **to 75** years of age ~~or older~~ (inclusive at the time of Screening) with T2DM

#### Inclusion Criterion 2:

HbA1c  $\geq 7.0\%$  and  $\leq 9.05\%$  at Screening. If the first screening HbA1c does not meet the eligibility criterion, the HbA1c value may be checked up to 2 times during Screening, and if the average of these determinations meets the criterion, the subject ~~can be randomly assigned to treatment~~ **may be eligible for further participation in the study**

#### Inclusion Criterion 3:

Note: Subject should not have received any other antidiabetic medication within 30 days before Screening (e.g., GLP-1R agonist, dipeptidyl peptidase-IV inhibitor, SU, **meglitinide, sodium-glucose transporter 2 inhibitor,** or thiazolidinedione). Subjects receiving commercially available premixed basal and prandial insulin are not eligible for this study.

#### Inclusion Criterion 4:

Fasting C-peptide  $\geq 0.8$  ng/mL ( $\geq 0.26$  nmol/L). **If the fasting C-peptide is  $< 0.8$  ng/mL ( $< 0.26$  nmol/L) but stimulated C-peptide 90 minutes after a standardized mixed meal is  $\geq 1.5$  ng/mL ( $\geq 0.5$  nmol/L), the subject may be eligible for further participation in the study** [Jones, 2013; Maldonado, 2005]

**Note: Plasma glucose will also be measured 90 minutes after the standardized mixed meal; if the concurrent plasma glucose collected 90 minutes after the standardized**

**mixed meal is not  $\geq 144.0$  mg/dL ( $\geq 8.0$  mmol/L), the stimulated C-peptide test may be repeated during an unscheduled visit.**

**Inclusion Criterion 7:**

Male partner sterilization prior to the **female subject's entry** into the study, and this male is the sole partner for that subject. The information on the male sterility can come from the site personnel's review of **the female** subject's medical records, medical examination of the subject and/or semen analysis, or interview with the **female** subject on **her male partner's** ~~his~~ medical history.

...

Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository) **[Hatcher, 2007]**

**Inclusion Criterion 8:**

Willing and able to comply with all study procedures, including performance of frequent SMBG profiles **and use of an e-diary**, according to the protocol

**Inclusion Criterion 9:**

Able and willing to provide written informed consent **after a thorough explanation of the study by the investigator or designee, which will include the opportunity for the subjects to ask questions**

**Inclusion Criterion 10:**

**Suitable for participation in a treat-to-target study, including intensified basal-bolus insulin therapy utilizing the prespecified glycemic targets defined in the protocol**

**Exclusion Criterion 7:**

History of ~~severe~~ hypoglycemia unawareness **(i.e., the absence of autonomic warning symptoms before the development of neuroglycopenic symptoms such as blurred vision, difficulty speaking, feeling faint, difficulty thinking, and confusion)**

**Exclusion Criterion 9:**

9. Clinically significant CV and/or cerebrovascular disease within 3 months before Screening including, but not limited to, the following:

- Stroke or transient ischemic attack
- Acute coronary syndrome (myocardial infarction [MI] or unstable angina not responsive to nitroglycerin)
- Cardiac surgery or percutaneous coronary procedure
- ~~Current or history of heart failure (New York Heart Association class III or IV)~~



**10. Any history of New York Heart Association class III or IV heart failure****Section 4.4, Additional Inclusion Criteria for Randomization:**

- **HbA<sub>1c</sub>  $\geq 7.0\%$  and  $\leq 9.0\%$  at Week -1. If the subject does not qualify for randomization based on this criterion, the assessment may be repeated on a weekly basis for a maximum of 2 additional weeks before randomization. The mean of all HbA<sub>1c</sub> assessments (Week -1 plus the additional HbA<sub>1c</sub> assessments) must be  $\geq 7.0\%$  and  $\leq 9.0\%$  for the subject to be eligible for randomization (see Section 4.6). Note: If a subject has confirmed (by a central laboratory) HbA<sub>1c</sub>  $< 7.0\%$  and  $> 9.0\%$  at Week -1 or the subject decides not to continue repeat testing, he or she will be considered a standardization failure (see Section 4.6)**

**Section 4.5, Withdrawal Criteria**

Every effort should be made to keep subjects in the study. The reasons for subjects not completing the study will be recorded.

~~A subject may be withdrawn from the study for the following reasons:~~

- ~~• AE, which, in the opinion of the investigator precludes effective participation of the subject or poses a safety concern~~

The following ~~AEs will~~ require withdrawal from the study:

- **AE, which, in the opinion of the investigator precludes effective participation of the subject or poses a safety concern**
- Elevation of liver function test results ~~according to~~ **meeting any of** the liver stopping criteria (see Section 6.3.6)
- Severe allergic/hypersensitivity reaction that is considered by the investigator to be attributable to randomized study medication or without a likely alternative etiology (see Section 6.3.9.3)
- Confirmed acute or chronic pancreatitis (see Section 6.3.9.4)
- Confirmed medullary thyroid cancer (see Section 6.3.9.6)
- ~~Severe~~ **Recurrent severe** hypoglycemia or recurrent nocturnal hypoglycemia during the Treatment Period posing a potential risk to the subject, as judged by the investigator
- **Pregnancy or intention of becoming pregnant**
- **Major protocol deviation if withdrawal from the study is mandated by the medical monitor (the investigator should discuss the protocol deviation with the medical monitor before withdrawing study medication)**
- **GSK-defined Sentinel Event. The medical monitor will advise the investigator if an SAE meets the criteria of a true Sentinel Event (e.g.,**

**without a clear alternate etiology) for which withdrawal is required (see Section 6.3.7.3)**

**In addition, a subject may be withdrawn from the study for the following reasons:**

- FPG >270 mg/dL (15.0 mmol/L) at least 8 weeks after randomization on 3 consecutive days (by blood glucose meter), which is confirmed by a central laboratory (to be done within 2 weeks of the home glucose monitoring). Continuation of the subject will be at the discretion of the investigator after consultation with the medical monitor
- Lost to follow-up
- Study closed/terminated or investigator site closed (where subject transfer to another site is not possible)
- ~~Pregnancy or intention of becoming pregnant~~
- ~~Major protocol deviation (the investigator should discuss the protocol deviation with the sponsor before withdrawing study medication)~~
- Subject decision (reason to be documented in the electronic case report form [eCRF], if specified by the subject)
- Investigator discretion

Note: Use of a prohibited medication constitutes a protocol deviation. Continuation of the subject in the study will be discussed with the medical monitor, and the decision of continuation or withdrawal will be documented.

#### **Section 4.6, Screening/Standardization Failures**

Screen failures are defined as subjects who consent to participate in the clinical trial but **do not meet all inclusion (Section 4.2) and exclusion (Section 4.3) criteria to continue in Screening. are never subsequently randomly assigned to treatment. Subjects failing to meet eligibility criteria may be rescreened after 2 weeks, as appropriate.** In order to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities, a minimal set of screen failure information will be collected including demography, screen failure details, eligibility criteria, and any SAEs.

**Standardization failures are defined as subjects who begin the Standardization Period but do not complete the Standardization Period or subsequently fail the Additional Inclusion Criteria for Randomization criteria (Section 4.4), or subjects who decide not to continue repeat testing. Standardization failures may not be rescreened.** ~~may be rescreened after 2 weeks, as appropriate. Subjects may then be randomly assigned provided they now meet the randomization criteria (Section 4.4) and still meet all of the inclusion criteria (Section 4.2) and none of the exclusion criteria (Section 4.3).~~

## Section 5.1.1, Dosing Guidance During the Standardization Period

### Insulin glargine

- If the subject's prestudy basal insulin is a once-daily regimen, transfer the subject to insulin glargine (subcutaneous injection) once daily at bedtime on a unit-per-unit basis. Note: **At the discretion of the investigator, it is permissible to reduce the insulin glargine dose by up to 10%.** ~~If subject is transferring from insulin detemir, it is permissible to reduce the insulin glargine dose by 10% at the discretion of the investigator.~~
- If the subject's prestudy basal insulin is given twice daily, then the subject's insulin glargine should be started once daily at bedtime at a dose that is 20% lower than the total daily prestudy basal dose.

During the Standardization Period, insulin glargine may be adjusted to achieve glycemic targets as close to normal as possible without untoward hypoglycemia in accordance with product labeling in the respective country and standards of care at the study center. **The treat-to-target titration algorithm for insulin glargine (Section 5.1.3.2, Table 3) is intended for use only during the Treatment Period.**

### Insulin lispro

- If the subject's current regimen of bolus insulin is administered at each of the 3 main meals, transfer the subject's therapy to insulin lispro on a unit-for-unit basis. **Note: At the discretion of the investigator, it is permissible to reduce the insulin lispro dose by up to 10%.**
- If the subject's current regimen of bolus insulin is administered ~~more less than~~ **3 times per day** or ~~less more~~ than 3 times **per day daily**, calculate the total daily bolus dose and divide it into 3 equal doses. ~~Transfer the subject to insulin lispro on a unit-for-unit basis based on the calculated dose to be administered with each of the 3 main meals.~~ **Alternatively, at the discretion of the investigator, if felt to be clinically preferable, it is permissible to allocate different starting doses of insulin lispro to each of the 3 main meals, maintaining the same total daily bolus dose.**

During the Standardization Period, insulin lispro may be adjusted to achieve glycemic targets as close to normal as possible without untoward hypoglycemia in accordance with product labeling in the respective country and standards of care at the study center. **The treat-to-target titration algorithm for insulin glargine (Section 5.1.3.2, Table 3) is intended for use only during the Treatment Period.**

## Section 5.1.3, (title change) Dose Titration During the Treatment Period

### Section 5.1.3.1, Albiglutide Titration

New text: **Note: In this study, downtitration of albiglutide 50 mg weekly to 30 mg weekly is not permitted.**

### Section 5.1.3.2, Insulin Titration

The intent of the American Diabetes Association and the European Association for the Study of Diabetes consensus statement for the treatment of T2DM is to maintain fasting and preprandial glucose values as close to a normal range as possible without untoward hypoglycemia **or other adverse effects of treatment [Inzucchi, 2015; Inzucchi, 2012; Nathan, 2008; Nathan, 2006]. Less stringent HbA<sub>1c</sub> goals are appropriate for other subjects, such as those with a history of severe hypoglycemia, limited life expectancy, advanced complications, or extensive comorbid conditions.**

#### Insulin Glargine Titration

Both treatment groups will follow the same insulin glargine titration algorithm during the Treatment Period.

**The main focus for the initial insulin titration should be on the basal insulin given before bedtime. Although optimization of insulin glargine should continue throughout the Treatment Period, it is expected that the basal insulin dose will have been stabilized for all subjects after about 6 weeks.**

**Prior to each study visit and telephone contact during the Treatment Period, a recommended dose of insulin glargine will be based on the mean of the subject's last 3 available before breakfast SMBG values (at least 2 of which are consecutive) and the titration algorithm for insulin glargine provided in Table 3. It is important that the investigator use his or her medical judgment in determining whether or not the algorithm recommended dose adjustment is appropriate for a particular subject at each time point. Of importance, decisions should be made taking into consideration all available information, such as symptoms of hypoglycemia or hyperglycemia, current total daily dose of insulin, and previous responses to dose adjustments, as well as additional glucose measurements (lowest of the last 3 SMBG values, other SMBG values in the week preceding the dose adjustment decision, or FPG [from a central laboratory]).**

~~The titration of insulin glargine is based on the mean of the subject's SMBG values measured before breakfast from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact, as shown in Table 3.~~

If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of SMBG measurements in this treat to target study.

**Table 3, Titration Algorithm for Recommended Insulin Glargine Dose Adjustment**

| Before Breakfast Blood Glucose <sup>1</sup>                                                                                                                                        |                        | Adjustment of Insulin Glargine (IU) <sup>2</sup>                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|---------------------------------------------------------------------------|
| mg/dL                                                                                                                                                                              | mmol/L                 |                                                                           |
| <56 <sup>3</sup>                                                                                                                                                                   | <3.1 <sup>3</sup>      | -4<br>For a dose >50 U, consider 10% dose reduction                       |
| 56 – 69 <sup>3</sup>                                                                                                                                                               | 3.1 – 3.8 <sup>3</sup> | -2<br>For a dose >50 U, consider 5% dose reduction                        |
| 70 – 79                                                                                                                                                                            | 3.9 – 4.4              | -1                                                                        |
| 80 – 109 <sup>3</sup> = Target                                                                                                                                                     | 4.5 – 5.5 = Target     | No adjustment                                                             |
| 110 – 129                                                                                                                                                                          | 5.6 – 6.6              | +2                                                                        |
| 130 – 149                                                                                                                                                                          | 6.7 – 7.7              | +4                                                                        |
| 150 – 169                                                                                                                                                                          | 8.3 – 9.4              | +6                                                                        |
| ≥170                                                                                                                                                                               | ≥9.4                   | +8                                                                        |
| <b>If severe hypoglycemia (requiring assistance) or any other clinically significant hypoglycemia (e.g., nocturnal hypoglycemia) was documented since the last dose adjustment</b> |                        | <b>Decrease insulin dose 10% to 15%, at the investigator's discretion</b> |

1. Mean of measurements from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of self-monitored blood glucose measurements.
2. Modified based on the insulin titration algorithms in the BEGIN basal-bolus type 2 study [Garber, 2012] and other published treat-to-target studies [Rosenstock, 2008; Abrahamson, 2012; Mathieu, 2014; Riddle, 2014].
3. Investigator may defer adjustment if there is an obvious reason for the low value such as a missed meal.

The algorithm in Table 3 should be followed at all visits and telephone contacts during the Treatment Period. However, it is also important that the investigator base the decision to adjust the insulin dose on all available information, such as symptoms of hypoglycemia or hyperglycemia, previous responses to dose adjustments, as well as additional glucose measurements (FPG [from a central laboratory] or SMBG) other than the mandatory ones. Any **insulin titration that differs** deviation from the algorithm **recommended dose** must be commented on by the investigator and the reason documented on the appropriate page of the eCRF. **If adequate documentation is not provided in the eCRF, a protocol deviation will be recorded; any deviation that does not have a valid reason, as detailed above, will be recorded as a protocol deviation.**

The main focus for the initial insulin titration should be on the basal insulin given before bedtime. After about 6 weeks, it is expected that the basal insulin dose will have been optimized for all subjects.

For those subject's randomly assigned to the albiglutide plus insulin glargine group, the optimization of insulin glargine should continue throughout the Treatment Period. If the before breakfast glucose target has been achieved, but it is felt that the basal insulin needs further optimization, then alternatives (e.g., moving the basal injection to the morning or splitting the basal dose into twice daily injections) can be discussed with the medical monitor overseeing the titration and documented.

## Insulin Lispro Titration

**Insulin titration should start with insulin glargine given before bedtime. After about 6 weeks, it is expected that the basal insulin glargine dose will have been stabilized and the insulin lispro titration may begin.**

Following randomization to study medication, insulin lispro will be titrated differently in each treatment group.

In the albiglutide plus insulin glargine group, the insulin lispro dose will be downtitrated at the Baseline/Randomization visit to half that used at the end of the Standardization Period. At Week 4, insulin lispro will be completely discontinued and should remain discontinued for the remainder of the Treatment Period; unless the subject meets the criteria for insulin lispro re-introduction (see Section 5.1.3.5).

In the insulin glargine plus insulin lispro treatment group, the dose adjustment of insulin lispro **given in association with a meal** is based on **the blood glucose measurements taken prior to the subsequent meal. Therefore, blood glucose measurements taken Prior to Lunch are utilized to adjust the dose of insulin lispro taken with breakfast, the blood glucose measurements taken Prior to Dinner are utilized to adjust the dose of insulin lispro taken with lunch, and the blood glucose measurements taken Prior to Bedtime are utilized to adjust the dose of insulin lispro taken with dinner** ~~**the post-breakfast (prior to lunch), post-lunch (prior to dinner), or post-dinner (i.e., bedtime) blood glucose value.**~~ **Following Baseline/Randomization,** ~~the main focus~~ for the initial insulin titration should be on the basal insulin before considering changes in the bolus insulin, unless the investigator finds it absolutely necessary to adjust the bolus insulin first.

~~It is recommended that dose adjustments of insulin lispro be made on the mean of values from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact (Table 4).~~ **Prior to each study visit and telephone contact during the Treatment Period, a recommended dose of insulin lispro for each specific meal will be based on the mean of the subject's last 3 available preprandial SMBG values (at least 2 of which are consecutive) and the titration algorithm for insulin lispro provided in Table 4. It is important that the investigator use his or her medical judgment in determining whether or not the algorithm recommended dose adjustment is appropriate for a particular subject at each time point. Of importance, decisions should be made taking into consideration all available information, such as symptoms of hypoglycemia or hyperglycemia, current total daily dose and distribution of insulin lispro doses, and previous responses to dose adjustments, as well as additional glucose measurements (lowest of the last 3 SMBG values, other SMBG values in the week preceding the dose adjustment decision, or FPG [from a central laboratory]) other than the mandatory ones.**

If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact, unless in the investigator's judgment, a dose adjustment is warranted at that time. The subject should be retrained on the importance of SMBG measurements in this treat to target study.

**Table 4, Titration Algorithm for Recommended Insulin Lispro Dose Adjustment**

| <u>Post-breakfast Prior to Lunch, Post-lunch Prior to Dinner, Prior to Bedtime</u><br><u>Post-dinner Blood Glucose<sup>1</sup></u>                  |                                                    | Adjustment of Lispro Insulin (U) <sup>2</sup>                                                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| mg/dL                                                                                                                                               | mmol/L                                             |                                                                                                                                          |
| <del>≤99&lt;70</del> without obvious explanation                                                                                                    | <del>≤5.5&lt;3.9</del> without obvious explanation | <del>-1 to -2<sup>3</sup></del><br><b>For a dose &gt;50 U, consider a 5% to 10% dose reduction at the discretion of the investigator</b> |
| <del>100 - 119</del> 70 - 99 = Target                                                                                                               | <del>5.6 - 6.6</del> 3.9 - 5.5 = Target            | No adjustment                                                                                                                            |
| <del>120-140</del> - 139                                                                                                                            | <del>6.7-7.7</del> 5.6 - 7.7                       | +2                                                                                                                                       |
| 140 - 179                                                                                                                                           | 7.8 - 9.9                                          | +3                                                                                                                                       |
| ≥180                                                                                                                                                | ≥10.0                                              | +4                                                                                                                                       |
| <b>If severe hypoglycemia (requiring assistance) or any other clinically significant hypoglycemia was documented since the last dose adjustment</b> |                                                    | <b>Decrease insulin dose at the investigator's discretion (i.e., 10% to 15%)</b>                                                         |

1. Mean of measurements from the last 3 available days (at least 2 of which are consecutive) in the week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact, unless in the investigator's judgment, a dose adjustment is warranted at that time. The subject should be retrained on the importance of self-monitored blood glucose measurements (SMBG). ~~Note: post-breakfast (prior to lunch), post-lunch (prior to dinner), post-dinner (i.e., bedtime).~~
2. Modified based on the insulin titration algorithms in the BEGIN basal-bolus type 2 study [Garber, 2012] and other published treat-to-target studies [Rosenstock, 2008; Abrahamson, 2012; Mathieu, 2014; Riddle, 2014].
3. **For subjects with an SMBG value less than 70 mg/dL without obvious explanation, At the investigator's discretion, insulin lispro may be stopped at the investigator's discretion.**

~~The algorithm in Table 4 should be followed at all visits and telephone contacts during the Treatment Period. However, similar to the titration of insulin glargine, it is also important that the investigator base the decision to adjust the insulin dose on all available information, such as symptoms of hypoglycemia or hyperglycemia, previous responses to dose adjustments, as well as additional glucose measurements (FPG [from a central laboratory] or SMBG) other than the mandatory ones. Any deviation from the algorithm must be commented on by the investigator and the reason documented on the appropriate page of the eCRF; any deviation that does not have a valid reason, as detailed above, will be recorded as a protocol deviation. Any insulin titration that differs from the algorithm recommended dose must be commented on by the investigator and the reason must be documented on the appropriate page of the eCRF. If adequate documentation is not provided in the eCRF, a protocol deviation will be recorded.~~

### **Section 5.1.3.3, (new section) Intensive Subject Glycemic Surveillance and Management**

**In this treat-to-target study, which includes the discontinuation of prandial insulin in subjects randomly allocated to the albiglutide plus insulin glargine treatment arm as well as the intensification of basal-bolus insulin in subjects randomly allocated to the insulin glargine plus insulin lispro treatment arm, it is important that subjects receive adequate diabetic patient education and training and detailed clear explanations regarding all required study procedures related to glycemic management (see Section 6.2.4 and Section 6.2.5). It is also imperative that study**

**investigators closely monitor available subject information and apply prompt medical judgment as necessary to maintain appropriate glycemic control.**

**To facilitate subject surveillance by the study investigator, the investigator will have access to information collected in the subject's e-diary, such as daily SMBG measurements (see Section 6.2.2), daily insulin use (see Section 6.2.5), and subject-reported hypoglycemia (see Section 6.3.1). In addition, study investigators will receive notification of extreme SMBG measurements (i.e., SMBG measurements  $\leq 50$  mg/dL [ $\leq 2.8$  mmol/L) and SMBG between 50 to 60 mg/dL (2.8 to 3.3 mmol/L)], as well as episodes of severe hypoglycemia recorded in the subject's e-diary. Additional details on these tools are provided in the accompanying SPM.**

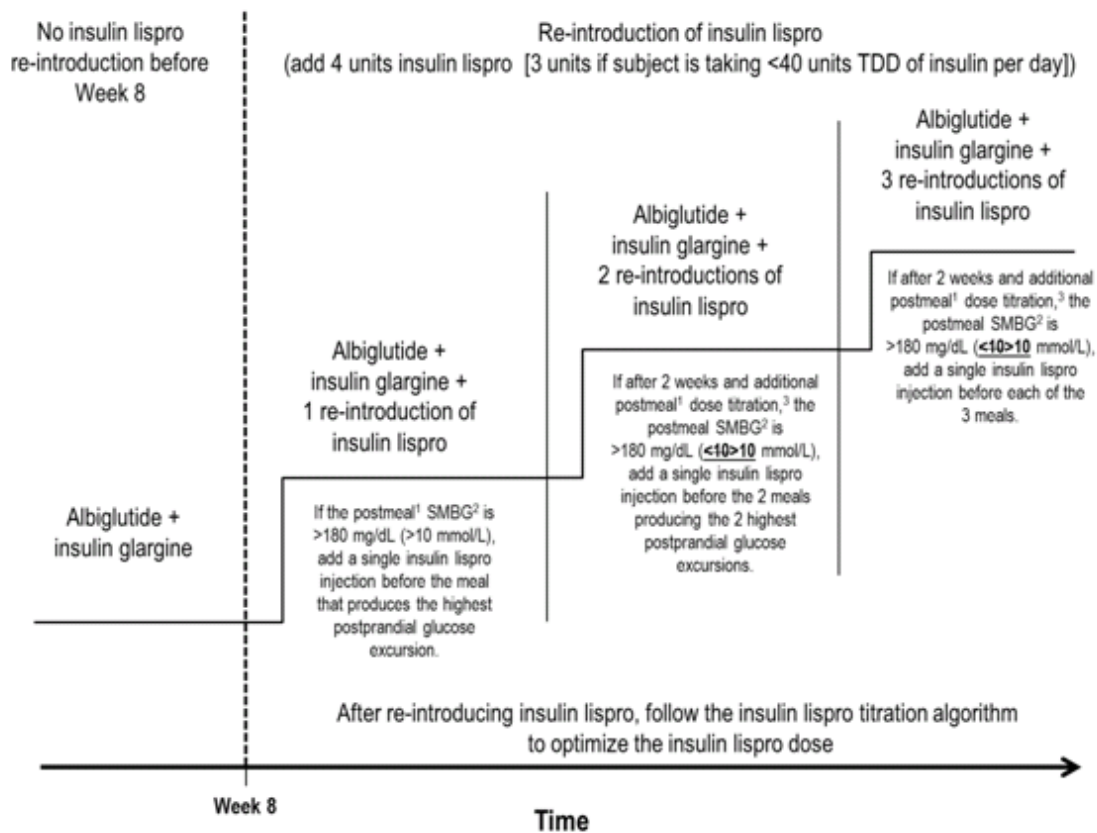
#### **Section 5.1.3.4, (title change) Documentation Surveillance of Insulin Titration**

Surveillance of insulin titration **and documentation** will be performed centrally. Within approximately **3 business days** ~~24 hours~~ after a subject's study visit/telephone contact, the investigator must ensure that the following data are available for review by GSK/PPD:

- Comments on any deviation to the insulin titration algorithms **must be entered into the eCRFs**

The data regarding titration deviations will be reviewed by GSK/PPD. Based on this information, an inquiry as to why the investigator chose to deviate from the titration algorithm may be made, particularly when details of any SMBG readings, time, and date, or hypoglycemic symptoms used in such a decision are **not provided or lack clarity needed**. Not all deviations will lead to inquiry. When the investigator receives an inquiry, a response with the reasons for not adhering to the titration guideline should be sent to GSK/PPD within approximately 3 days. Depending on the response, additional inquiries may be sent.



**Figure 2, Re-introduction Algorithm for Insulin Lispro**

HbA<sub>1c</sub> = glycosylated hemoglobin. SMBG = self-monitored blood glucose.

Note: Figure modified with permissions (pending) from [Abrahamson 2012].

1. Post-breakfast (~~p~~Prior to Lunch), post-lunch (~~p~~Prior to dinner), or post-dinner (i.e., Prior to Bedtime).
2. Mean of measurements from the last 3 available days (at least 2 of which are consecutive) in week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of SMBG measurements.
3. For insulin lispro dose titration, see Section 5.1.3.2, Table 4.

## Section 5.5, Treatment Compliance

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

## Section 5.6.2, Prohibited Medications and Nondrug Therapies

- Any oral antidiabetic medications (e.g., GLP-1R agonist, dipeptidyl peptidase-IV inhibitor, SU, thiazolidinedione, **meglitinide, sodium-glucose transporter 2**)

inhibitor, or commercially available premixed basal and prandial insulin) other than the treatment they have been randomly assigned to, insulin glargine, insulin lispro, and their current regimen of background metformin, if applicable, being taken at Screening.

**Section 5.7, (title change) Treatment Between Week 26 (End of Treatment)/Early Withdrawal and After the Follow-up Visit ~~End of the Study~~**

**Section 5.7.1, (new section) Treatment Between Week 26 (End of Treatment)/Early Withdrawal and Follow-up**

After completion of the end-of-treatment (Week 26) or Early Withdrawal visits, subjects will return to the study center in 4 weeks for the Follow-up visit. During this time, subjects will continue insulin glargine or insulin glargine plus insulin lispro to maintain adequate glycemic control.

For subjects in the albiglutide plus insulin glargine treatment arm, the last dose of once-weekly albiglutide will occur at Week 25. As needed, insulin lispro may also be re-introduced during this period according to the re-introduction of insulin lispro algorithm provided in Section 5.1.3.5. Insulin glargine alone (in subjects for whom insulin lispro has not been re-introduced) or insulin glargine and insulin lispro (in subjects for whom insulin lispro has been re-introduced) can be adjusted to achieve or maintain glycemic targets as close to normal as possible without untoward hypoglycemia in accordance with product labeling in the respective country and standards of care at the study center.

For subjects in the insulin glargine plus insulin lispro treatment arm, both insulin glargine and insulin lispro may be adjusted to achieve or maintain glycemic targets as close to normal as possible without untoward hypoglycemia in accordance with product labeling in the respective country and standards of care at the study center.

Note: During this time, subjects must not use any prohibited medications or nondrug therapies (see Section 5.6.2).

**Table 5, Time and Events Table – Study Visits**

Dispense home glucose monitoring device and e-diary (title change only)

Collect e-diary from subject: added to Follow-up Visit

Provide advice on diet, exercise, and home glucose monitoring, and hypoglycemia advise: added to Early Withdrawal Visit

Review glucose monitoring with subject: added to Early Withdrawal Visit

Obtain daily insulin dose information: added to Early Withdrawal Visit

Check visual acuity and funduscopy: added to Early Withdrawal Visit

Obtain chemistry sample: added to Visit 3, Week -1

**Obtain simulated C-peptide sample 90 minutes after administration of a mixed-meal:** added to Visit 1

Assess investigational product **and other study treatment** compliance

Footnote 5: Standard diabetic dietary, exercise, and home blood glucose monitoring advice to be provided at Visit 2 (Week -4) and reinforced at each study site visit through the End-of- Treatment visit. Subjects will monitor their glucose according to instructions. The investigator will review the glucose meter readings and adjust insulin glargine and insulin lispro doses in accordance with product labeling in the respective country and standard of care at the study center during the Standardization Period and per Table 3 and Table 4, respectively, during the Treatment Period. **At each visit through the end-of-treatment visit (Visit 9; Week 26), subjects should be trained on the signs and symptoms of hypoglycemia, including nocturnal hypoglycemia, as well as the common causes of hypoglycemia. Subjects should also be educated on appropriate methods to help prevent hypoglycemia. It is also particularly important to advise subjects to contact the study site before any potential dietary change, as this may necessitate a change in insulin doses to avoid the development of hypoglycemia. Subjects should also be educated on how to treat hypoglycemia. For additional information, see Section 6.3.1.**

Footnote 10 added: **For the Screening assessment, a documented examination within six months of the Screening visit would also be acceptable but only when there was NO clinical change (e.g., decrease in visual acuity/visual field) since the last prior funduscopy. The end of treatment/early withdrawal assessment eye exam should be carried out by the investigator.**

Footnote 24 added: **As described in Section 3.1, an optional fasting HbA<sub>1c</sub> value may be determined using a Metrika kit or other finger-stick procedure to provide an initial guide of subject eligibility for investigators.**

Footnote 25 added: **If the HbA<sub>1c</sub> value at Week -1 is not  $\geq 7.0\%$  and  $\leq 9.0\%$ , the assessment may be repeated on a weekly basis for a maximum of 2 additional weeks before randomization. The mean of all HbA<sub>1c</sub> assessments (Week -1 plus the additional HbA<sub>1c</sub> assessments) must be  $\geq 7.0\%$  and  $\leq 9.0\%$  for the subject to be eligible for randomization. Note: If a subject has confirmed (by a central laboratory) HbA<sub>1c</sub>  $< 7.0\%$  and  $> 9.0\%$  at Week -1 or the subject decides not to continue repeat testing, he or she will be considered a standardization failure.**

Footnote 26 added: **Subjects will have both fasting C-peptide and stimulated C-peptide testing. If the fasting C-peptide is  $< 0.8$  ng/mL ( $< 0.26$  nmol/L) but stimulated C-peptide 90 minutes after a standardized mixed meal is  $\geq 1.5$  ng/mL ( $\geq 0.5$  nmol/L), the subject meets the C-peptide inclusion criterion.**

Footnote 28 updated: Insulin glargine and insulin lispro will be dispensed during the Standardization Period at Visit 2 (Week -4) with additional dispensing at Visit 3 (Week -1) optional as needed to ensure adequate supply up to Visit 4 (Week 0). Dispense albiglutide, insulin glargine, and insulin lispro, as appropriate, according to

randomization at Baseline/Randomization. See Section 5.7 for additional information regarding insulin usage after Week 26/Early Withdrawal.

#### **Table 6, Time and Events Table – Telephone Calls**

A Week 28 telephone call was added.

#### **Section 6.2.2.1, Home Blood Glucose Monitoring**

All subjects in the study should be instructed to measure and record blood glucose values from their glucose meter a minimum of 4 times per day at the following times (except prior to Baseline/Randomization, Week 10, and Week 26 where an 8-point SMBG profile will be performed; see Section 6.2.2.2):

- Before breakfast (at least 8 hours without food intake)
- ~~Post-breakfast (pPrior to L~~lunch}
- ~~Post-lunch (pPrior to D~~dinner}
- ~~Post-dinner (i.e., a~~At bBedtime}

#### **Section 6.3.1, Hypoglycemic Events**

Specific criteria for monitoring hypoglycemic events have been designed to ensure subject safety and to closely monitor hypoglycemia.

At each visit through the end-of-treatment visit (Visit 9; Week 26), subjects should be trained on the signs and symptoms of hypoglycemia (e.g., hunger, confusion, dizziness, anxiety, increased heart rate, visual disturbances), including nocturnal hypoglycemia (i.e., nightmares; night sweats; tired, irritable, or confused upon awakening), as well as the common causes of hypoglycemia. Subjects should also be educated on appropriate methods to help prevent hypoglycemia (i.e., strictly observe nutritional guidance from the physician or study site staff, consume small snacks before intense exercise, promptly communicate with the study site on “ill days” for additional guidance). It is also particularly important to advise subjects to contact the study site before any potential dietary change, as this may necessitate a change in insulin doses to avoid the development of hypoglycemia. Subjects should also be educated on how to treat hypoglycemia (e.g., oral glucose treatment with simple carbohydrates).

Subjects will be asked to report hypoglycemic events that occur between study visits using a diary. ~~Specific criteria for monitoring hypoglycemic events have been designed to ensure subject safety and to closely monitor hypoglycemia.~~ In this study, hypoglycemic events are defined according to recommendations by the American Diabetes Association and The Endocrine Society Workgroup on Hypoglycemia as follows [Sequist, 2013]. To aid correct classification and treatment of hypoglycemic events, subjects should be instructed to repeat SMBG measurements  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L).

### Section 6.3.5, Clinical Laboratory Testing

Other blood tests at time points specified in the Time and Events Table (Table 5):

- HbA<sub>1c</sub>
  - Note: As described in Section 3.1, an optional fasting HbA<sub>1c</sub> value may be determined using a Metrika kit or other finger-stick procedure to provide an initial guide of subject eligibility for investigators.
- Fasting C-peptide and stimulated C-peptide 90 minutes after a standardized mixed meal
- TSH. If TSH is above the ULN, free T4 (reflex) will also be measured
- Lipid panel: total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and free fatty acids
- Hepatitis B surface antigen
- Hepatitis C antibody. If hepatitis C antibody positive, an RNA polymerase chain reaction should be performed on the same sample to confirm the result

### Section 6.7 (new section), Tracking of Albiglutide Pen Injector Failures and User Errors

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

NOTE: Pen injector failures and user errors associated with or result in events fulfilling the definition of an AE or SAE will follow the processes outlined in Section 6.3.7.

### Section 8.3.3.1, Primary Comparisons of Interest

.... Further details of the sensitivity analysis, including imputation methods and assumptions about the missing data, ~~are described in Section 8.3.5.1~~ ~~will be provided in the RAP.~~

#### 8.3.5.1.1 Impact of Missing Data on Primary Endpoint

Missing data are not explicitly imputed in the primary MMRM analysis; although, there is an underlying assumption that data are missing at random, including those withdrawn for lack of efficacy. All available scheduled postbaseline assessments up to endpoint are utilized and, via modelling of the within subject correlation structure, the derived treatment difference at Week 26 is adjusted to take into account missing data. The MMRM analysis (using saturated fixed effects and an unstructured variance-covariance matrix) is considered appropriate as the primary

method of analysis, as it has been shown to give sensible answers to on-treatment questions in a range of practical situations [Siddiqui, 2009].

#### **8.3.5.1.2      Extent of Missing Primary Analysis Data**

Missing data is expected to arise mainly from subjects missing complete visits. The amount of missing data for those baseline covariates included in the statistical analysis is expected to be none or at worst minimal. If it should occur, that subject will effectively be lost to analysis. Missing data for HbA<sub>1c</sub> between two nonmissing visits will be considered missing at random (intermediate missing data).

In this study, subjects who withdraw from treatment will be withdrawn from the study. In the eCRF, the reason for treatment discontinuation and the reason for withdrawal from the study are collected separately. Whenever the HbA<sub>1c</sub> value at Week 26 is missing (end of the study), the reason can be determined based on available data in these two locations. The reason for missing data can be classified as follows: safety, procedural (including withdrawal of consent), or lack of efficacy.

#### **8.3.5.1.3      Reasons for Withdrawal**

Reasons for withdrawal are assumed to fall into three broad categories:

- Procedural (e.g., lost to follow-up, withdrew consent, protocol deviation, study closed/terminated, and investigator discretion): In this case, it is expected that an assumption of Missing at Random (MAR) is appropriate for imputation of HbA<sub>1c</sub> data after withdrawal.
- Safety (e.g., AE, subject reached protocol-defined stopping criteria): It is expected that, in most cases, any change in safety related to these reasons for withdrawal would have been captured prior to the subject withdrawing from the study. In Study GLP108486 (albiglutide versus lispro over background glargine), 5% of subjects in the albiglutide group and <1% in the lispro group had AEs leading to withdrawal of active treatment through Week 26. In the albiglutide group, the most common AE leading to withdrawal was injection site reaction (1.1%). Missing HbA<sub>1c</sub> values after withdrawal due to safety concerns will be considered to possibly be missing not at random (MNAR).
- Lack of efficacy: In this treat-to-target study, a substantial number of cases of withdrawal due to lack of efficacy is not expected. Missing HbA<sub>1c</sub> values after withdrawal due to lack of efficacy are considered to possibly be MNAR.

Sensitivity analyses will be performed for data missing due to safety concerns or due to lack of efficacy.

#### **8.3.5.1.4      Handling of Missing Data**

The impact of missing data will be explored, as outlined below, for the Full Analysis Population only.

### Examination of Missing Data Patterns

To examine the nature of missing data, cohorts of subjects will be defined based on the scheduled assessments (HbA<sub>1c</sub> change from Baseline) that were completed at Weeks 4, 5, 10, 18, 26.

1. Subjects who have week 4 assessment only
2. Subjects who have assessments up to and including Week 5 only
3. Subjects who have assessments up to and including Week 10 only
4. Subjects who have assessments up to and including Week 18 only
5. Subjects who have assessments up to and including Week 26.

The number and percentage of subjects on each treatment in the 5 cohorts defined here will be tabulated. Graphical methods will be used to examine changes from Baseline over time to assess the pattern of outcomes prior to withdrawal.

### Sensitivity Analyses – Multiple Imputation

Sensitivity analyses using multiple imputation methods will be conducted. Firstly, missing data between two nonmissing time points will be considered missing at random.

The following multiple imputation methods are proposed based on whether data are missing at random or not at random:

1. All missing data assumed MAR: Imputation is based on means and variances-covariances from subjects in the same treatment group as the withdrawn subject and is comparable to MMRM. The main differences are that this approach uses separate covariance parameter estimation for each arm, and also separate regression parameters are estimated on baseline covariates within each arm. This more complex parameterization of the imputation model compared with the analysis model is valid. This approach will be used for all data missing post withdrawal. Here the estimand is one where after withdrawal all subjects progress in a similar way to those who remain in the trial. We expect the MMRM and this to give similar answers. If so, then it indicates any difference between the primary MMRM analysis and multiple imputation sensitivity analysis is due to the assumed effect modification and the assumed rates of HbA<sub>1c</sub> increase after withdrawal, rather than anything to do with going from an MMRM approach to a multiple imputation approach.
2. Missing due to lack of efficacy or due to safety concerns using Last Mean Carried Forward (LMCF), that is MNAR: This approach assumes that a constant rate of increase in HbA<sub>1c</sub> change from Baseline is experienced by subjects following withdrawal from the study for lack of efficacy or due to safety concerns. The MAR approach will be used for missing data due to procedural reasons. Sensitivity analyses using the LMCF approach will be performed using the following rates of HbA<sub>1c</sub> increase: 0%/month, 0.1%/month, and 0.2%/month to explore the potential impact as in a tipping-point analysis.

For each treatment group, these 3 rates will be assumed, resulting in 9 scenarios. The resulting treatment differences and associated P-values for noninferiority will be tabulated against the varying rates of HbA<sub>1c</sub> increase. This estimand is one where those who withdraw for lack of efficacy or safety concerns are assumed to revert to an unstable treatment regimen with an increasing rate of HbA<sub>1c</sub>.

For each imputation data set, an analysis of variance will be carried using Week 26 data, both actual and imputed, using the same covariates as in the primary analysis. Contrasts of interest will be estimated and then combined across imputations using standard multiple imputation rules.

Additional scenarios for sensitivity analysis may be added and described in the RAP.

## **Section 9.2, Regulatory and Ethical Considerations, Including the Informed Consent Process**

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding ethical principles of the current version of that are outlined in the Declaration of Helsinki 2008 (based on the initial version accepted in 1996), including, but not limited to:

- IRB/IEC review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

## **Section 10.0, References**

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## Protocol Amendment Number 02

Protocol Amendment Number 02 is applicable only to clinical study centers in Germany who are participating in this study. The rationale for these changes is based on the explicit request of a German ethics committee. Protocol changes specified in Amendment Number 02 are summarized as follows:

- Inclusion criterion 7 was updated to indicate that progestogen-only pills are acceptable only if they have a Pearl Index of less than 1.0
- Exclusion criterion 21 was added to exclude persons who have been put in an institution because of official or legal order
- Exclusion criterion 22 was added to exclude employees (or the employee's relatives) of the sponsor, the contract research organization, or the investigative site

### Specific Changes in the Text

#### Section 4.2, Inclusion Criteria

7. Female subjects of childbearing potential (i.e., not surgically sterile and/or not postmenopausal) must be practicing adequate contraception (as defined below) for the duration of participation in the study including the 4-week Posttreatment Follow-up Period
  - Abstinence from penile-vaginal intercourse, when this is the female's preferred and usual lifestyle
  - Oral contraceptive, either combined or progestogen alone  
**Note: For subjects participating at sites in Germany, progestogen-only pills are only acceptable if they have a Pearl Index of less than 1.0 (e.g., those containing 75 µg desogestrel)**
  - Injectable progestogen
  - Implants of etonogestrel or levonorgestrel
  - Estrogenic vaginal ring
  - Percutaneous contraceptive patches
  - Intrauterine device or intrauterine system that has a failure rate of less than 1% per year when used consistently and correctly as stated in the product label
  - Male partner sterilization prior to the **female subject's entry** into the study, and this male is the sole partner for that subject. The information on the male sterility can come from the site personnel's review of the female subject's medical records, medical examination of the subject and/or semen analysis, or interview with the female subject on her male partner's medical history.

- Male condom **combined with a female diaphragm**, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007]

#### **Section 4.3, Exclusion Criteria**

21. **(New) Persons who have been put in an institution because of official or legal order.**
22. **(New) Employees (or the employee's relatives) of the sponsor, the contract research organization, or the investigative site, including the investigator or other site staff.**

## Protocol Amendment Number 03

Protocol Amendment Number 03 is applicable to all clinical study centers participating in this study; where applicable, country-specific requirements have also been incorporated into this amendment. The Germany-specific changes outlined in Amendment 2 are included, specified for German sites only, and summarized in Section 11.5.1. French-specific study requirements are summarized in Section 11.5.2. In addition, changes that apply to all study centers are shown in Table 3 edits. Table 3 was edited for to correct select serum glucose concentrations for the insulin titration algorithm. Previously, changes had been made to select glucose concentrations in conventional units (i.e., mg/dL) but the corresponding changes to select glucose concentrations in SI units (mmol/L) were inadvertently missed. Therefore, the corrected values have been added for the corresponding mmol/L concentrations.

Protocol changes specified in Amendment Number 03 are summarized as follows:

- Exclusion Criteria 21 and 22 were noted as being specific to subjects participating at German study sites.
- Table 3 select blood glucose target concentrations (mmol/L) were corrected to the appropriate values
- Section 11.5: Country-specific study requirements were added for Germany and France.
- Incorporated other administrative changes to correct typographical errors and defined new abbreviations implemented with this amendment

### Specific Changes in the Text:

#### Title Page

Authors: PPD

### SPONSOR SIGNATORY

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Molly C Carr, Monica Shaw, MD  
~~Leader, Global Medical Affairs~~ VP Global Specialty  
Franchise Medical Head  
GlaxoSmithKline

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Date

## List of Abbreviations

|             |                                                                            |
|-------------|----------------------------------------------------------------------------|
| <u>ANSM</u> | <u>Agence nationale de sécurité du médicament et des produits de santé</u> |
| <u>CNIL</u> | <u>Commission nationale de l'informatique et des Libertés</u>              |
| <u>CRA</u>  | <u>clinical research assistant</u>                                         |
| <u>CTR</u>  | <u>clinical trial registry</u>                                             |
| <u>IT</u>   | <u>Information technology</u>                                              |

### Section 4.2 Inclusion Criteria #7

- Note: For subjects participating at sites in Germany: progestogen-only pills are only acceptable if they have a Pearl Index of less than 1.0 (e.g., those containing 75 µg desogestrel)
- Male partner sterilization prior to the ~~female subject's entry~~ female subject's entry into the study, and this male is the sole partner for that subject. The information on the male sterility can come from the site personnel's review of the female subject's medical records, medical examination of the subject and/or semen analysis, or interview with the female subject on her male partner's medical history.
- Male condom ~~combined with a female diaphragm~~ combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository)

### Section 4.3 Exclusion Criteria

The following additional exclusion criteria apply for subjects participating at sites in Germany:

21. Persons who have been put in an institution because of official or legal order
22. Employees (or the employee's relatives) of the sponsor, the contract research organization, or the investigative site, including the investigator or other site staff

### Section 4.4 Additional Inclusion Criteria for Randomization

If a subject has confirmed (by a central laboratory) HbA<sub>1c</sub> <7.0% and or >9.0% at Week - 1 or the subject decides not to continue repeat testing, he or she will be considered a standardization failure (see Section 4.6)

### Section 5.1.1 Dosing Guidance During the Standardization Period

#### Insulin lispro

- If the subject's current regimen of bolus insulin is administered at each of the 3 main meals, transfer the subject's therapy to insulin lispro on a unit-for-unit basis. Note: At the discretion of the investigator, it is permissible to reduce the **total daily** insulin lispro dose by up to 10%.
- If the subject's current regimen of bolus insulin is administered less than 3 times per day or more than 3 times per day, calculate the total daily bolus dose and divide it into 3 equal doses, administered with each of the 3 main meals. Alternatively, at the discretion of the investigator, if felt to be clinically preferable, it is permissible to allocate different starting doses of insulin lispro to each of the 3 main meals, maintaining the same total daily bolus dose. **Note: As above, at the discretion of the investigator, it is permissible to reduce the total daily insulin lispro dose by up to 10%.**

### Section 5.1.3.2 Insulin Titration

**Table 3 Titration Algorithm for Recommended Insulin Glargine Dose Adjustment**

| Before Breakfast Blood Glucose <sup>1</sup>                                                                                                                                 |                                          | Adjustment of Insulin Glargine (IU) <sup>2</sup>                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|--------------------------------------------------------------------|
| mg/dL                                                                                                                                                                       | mmol/L                                   |                                                                    |
| <56 <sup>3</sup>                                                                                                                                                            | <3.1 <sup>3</sup>                        | -4<br>For a dose >50 U, consider 10% dose reduction                |
| 56 – 69 <sup>3</sup>                                                                                                                                                        | 3.1 – 3.8 <sup>3</sup>                   | -2<br>For a dose >50 U, consider 5% dose reduction                 |
| 70 – 79                                                                                                                                                                     | 3.9 – 4.4                                | -1                                                                 |
| 80 – 109 = Target                                                                                                                                                           | 4.5 – <del>5.5</del> <b>6.0</b> = Target | No adjustment                                                      |
| 110 – 139                                                                                                                                                                   | <del>5.6</del> <b>6.1</b> – 7.7          | +2                                                                 |
| 140 – 179                                                                                                                                                                   | 7.8 – 9.9                                | +4                                                                 |
| ≥180                                                                                                                                                                        | ≥10.0                                    | +6                                                                 |
| If severe hypoglycemia (requiring assistance) or any other clinically significant hypoglycemia (e.g., nocturnal hypoglycemia) was documented since the last dose adjustment |                                          | Decrease insulin dose 10% to 15%, at the investigator's discretion |

### Section 5.1.3.5 Re-introduction of Insulin Lispro in the Albiglutide Treatment Group

Additionally, subjects not achieving a predefined threshold for glycemic control (confirmed persistent FPG  $\leq \geq 270$  mg/dL [15.0 mmol/L]) ~~at any time within~~ at least 8 weeks after randomization may be considered for study withdrawal based on the discretion of the investigator and the medical monitor (see Withdrawal Criteria in Section 4.5).

## Section 5.6.2 Prohibited Medications and Nondrug Therapies

Any ~~oral~~ antidiabetic medications (e.g., GLP-1R agonist, dipeptidyl peptidase-IV inhibitor, SU, thiazolidinedione, meglitinide, sodium-glucose transporter 2 inhibitor, or commercially available premixed basal and prandial insulin) other than the treatment they have been randomly assigned to, insulin glargine, insulin lispro, and their current regimen of background metformin, if applicable, being taken at Screening.

## Section 11.5 Appendix 5: Country-Specific Requirements

~~No country-specific requirements exist.~~

### Section 11.5.1 German-Specific Eligibility Requirements

Specific eligibility criteria were added for subjects participating at sites in Germany.

Section 4.2 includes German-specific text for inclusion #7 (bullet 2) stipulating that progestogen-only pills are only acceptable if they have a Pearl Index of less than 1.0 (e.g., those containing 75 µg desogestrel)

Section 4.3 includes German-specific text for exclusion #21 and #22 stipulating subjects are not eligible for study participation if they have been put in an institution because of official or legal order, or if they are employees (or the employee's relatives) of the sponsor, the contract research organization, or the investigative site, including the investigator or other site staff.

### Section 11.5.2 French Administrative Considerations and Specific Requirements

This appendix includes all the requirements of the French law (n° 2004-806 of 9th August 2004), and identifies, item per item, the mandatory modifications or additional information to the study protocol and includes specifics GSK requirements.

#### 1. Concerning the "STUDY POPULATION"

- In line with the local regulatory requirements, the following text in section "OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS" (Section 4.4) is added :

A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category.

It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

~~~~~

2. Concerning the “DATA ANALYSIS AND STATISTICAL CONSIDERATIONS” and specially in the “SAMPLE SIZE ASSUMPTION” (Section 8.2.1)

The expected number of patients to be recruited in France is declared to the French regulatory authority.

~~~~~

3. Concerning the “STUDY CONDUCT CONSIDERATIONS”

- In section “Regulatory and Ethical Considerations, Including the Informed Consent Process” (Section 9.2)

⇒ Concerning the process for informing the patient or his/her legally authorized representative, the following text is added :

French Patient Informed Consent form is a document which summarizes the main features of the study and allows collection of the patient's written consent in duplicate. It also contains a reference to the authorisation of Agence nationale de sécurité du médicament et des produits de santé (ANSM), the French National Agency for Medicines and Health Products Safety) and the approval from the French Ethic committee.

~~~~~

- In section concerning the “NOTIFICATION TO THE HOSPITAL DIRECTOR” (Section 9.2) the following text is added:

In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

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- In section concerning the “INFORMATION TO THE HOSPITAL PHARMACIST” (Section 9.2) the following text is added:

In accordance with Article R.1123-64 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the IB),



the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

~~~~~

- In section “DATA MANAGEMENT” (Section 7) the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GlaxoSmithKline Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through GlaxoSmithKline Laboratory (Clinical Operations Department).

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#### 4. Monitoring Visits (Section 9.3)

The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant (CRA) of GLAXOSMITHKLINE or of a service provider designated by GLAXOSMITHKLINE. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GLAXOSMITHKLINE or from a service provider designated by GLAXOSMITHKLINE. In addition, the Health Institution and the Investigator agree that the CRA or the service provider designated by GLAXOSMITHKLINE have direct access to all the data concerning the Study (test results, medical record, etc.). This consultation of the information by GLAXOSMITHKLINE is required to validate the data registered in the electronic Case Report Form (eCRF), in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

~~~~~

5. Data entry into the eCRF (Section 7)

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study’s eCRF use here below:

The Health Institution and the Investigator undertake:

- 1) That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the eCRF of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.
- 2) That the Investigator and the staff of the investigator center use the information technology (IT) Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
- 3) That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.
- 4) To keep the IT Equipment and/or access codes in a safe and secure place and to only authorize the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.
- 5) That the Investigator and the staff of the investigator center enter the data of the eCRF related to a patient visit in the 3 days following the date of the patient visit or, for the patient test results, in the 3 days following the reception of the results of such tests.
- 6) That the Investigator resolves and returns to GLAXOSMITHKLINE the data queries issued by GLAXOSMITHKLINE or a service provider designated by GLAXOSMITHKLINE within 7 days after the reception of the request of clarification or in a period of one (1) day during the final stage of clarification of the data base or in such other period as provided by GLAXOSMITHKLINE and/or a company designated by GLAXOSMITHKLINE.
- 7) To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
- 8) To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

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6. CTR Publication (Section 9.7)

It is expressly specified that GLAXOSMITHKLINE and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GLAXOSMITHKLINE GROUP named Clinical Trial Registry (CTR) including the registration of all the clinical trials conduct by the GLAXOSMITHKLINE Group and this before or after the publication of such results by any other process.

7. Data Protection French Law of 6 January 1987 (CNIL) (Section 9.7)

In accordance with the Data Protection French Law of 6 January 1978 as modified, computer files used by GLAXOSMITHKLINE to monitor and follow the implementation and the progress of the Study are declared with the Commission nationale de l'informatique et des Libertés (CNIL) by GLAXOSMITHKLINE. The Investigator has regarding the processing data related to him a right of access, of rectification and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GLAXOSMITHKLINE Group in France, Britain or United States, what the Investigator agrees by the signature of the present Protocol.

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