CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA: 125431	Submission Date(s): 01/11/2013
Brand Name	TBD
Generic Name	Albiglutide (GSK716155) Injection
Clinical Pharmacology Reviewer	Ritesh Jain, Ph.D.
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OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	GSK
Submission Type; Code	BLA 351; Standard
Formulation; Strength(s)	30-mg and a 50-mg single-use prefilled pen
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

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1 Executive Summary

Albiglutide is an agonist of the glucagon-like peptide receptor (GLP-1R). The proposed indication for albiglutide is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Albiglutide is intended to be administered 30 mg weekly as a subcutaneous (sc) injection. The dose may be increased to 50 mg weekly based on individual glycemic response.

Albiglutide is a recombinant fusion protein consisting of two copies of modified human glucagon like peptide-1 (GLP-1) genetically fused in series to human albumin (HA). The GLP-1 sequence has been modified with a glycine substituted for the naturally-occurring alanine at position 8 in order to confer resistance to dipeptidylpeptidase IV (DPP-IV) mediated proteolysis and extend the duration of action. In addition, the albumin moiety also extends the *in vivo* half-life of the molecule to 5 days allowing once weekly dosing.

Albiglutide for Injection is a 30 mg/dual chamber cartridge (DCC) pen injector or 50 mg/DCC pen injector, which is formulated as a prefilled, single dose product for sc administration of either 30 mg or 50 mg of albiglutide in a 0.5 mL injection volume.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted under BLA 125431 (dated 01/11/2013), and recommend approval of this application with the following recommendations:

1. OCP agrees with the sponsor proposed albiglutide dosing regimen of 30 mg weekly sc injection as the starting dose with an option to increase the dose to 50 mg weekly based on individual glycemic response.
2. Co-administration of albiglutide with simvastatin resulted in approximately 2 fold increase in peak plasma concentrations of active metabolite simvastatin acid. Since the clinical relevance of this change is not known, OCP proposes to use caution when initiating or escalating albiglutide doses in patients who are on simvastatin dose of 20 mg or greater (see section 1.3 and section 2.6.5).
3. OCP proposes that the albiglutide should be used with caution in patients with severe renal impairment (see section 2.3.5).

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The clinical program to support the proposed indication includes 23 clinical studies including 10 Phase I studies, 5 Phase II studies, and 8 Phase III studies.

Pharmacokinetics

In this application a typical human radiolabeled absorption, catabolism and excretion study has not been performed. The PK of albiglutide in T2DM subjects following single dose administration of 30 mg dose is summarized below:

Absorption: The absorption half-life of albiglutide following sc injection is approximately 1.5 days. Following sc administration of a single 30 mg dose to patients with type 2 diabetes, maximum concentrations were reached 3 to 5 days post dose with mean peak albiglutide concentration (C_{max}) of 1.74 µg/mL and mean area under the time-concentration curve (AUC_{inf}) of 465 µg•hr/mL. Similar exposure is achieved with sc administration of albiglutide in the abdomen, thigh, or upper arm. The absolute bioavailability of albiglutide following sc administration has not been evaluated.

Distribution: Following a single dose administration of albiglutide 30 mg in T2DM subjects, the mean estimate of apparent volume of distribution (V/F) was 11 L. As albiglutide is an albumin fusion molecule, plasma protein binding has not been evaluated.

Metabolism: Albiglutide is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Classical biotransformation studies have not been performed.

Elimination: Following sc administration albiglutide has a prolonged terminal half-life of approximately 5 days and steady-state exposures are achieved following 4 to 5 weeks of once-weekly administration.

Dose/Exposure-Response Efficacy: In this application, only one Phase 3 trial (GLP112756) provides information regarding the dose-response relationship of albiglutide. In this study, patients were randomized to either receive albiglutide 30 mg dose without up titration or to receive albiglutide 30 mg followed by up titration to 50 mg at week 12 (forced titration). There is a evidence of dose-response relationship for mean change from baseline in HbA1c in T2DM patients. As seen in Figure 10, there was a larger decline in HbA1c with increase in dose to 50 mg weekly compared to 30 mg weekly. Please refer to section 2.3.2 for further details on exposure-response relationship for efficacy.

Dose/Exposure-Response Safety: Study GLP112756 suggested no clear dose response relationship for safety endpoints. Since GLP112756 had a forced titration design, there are three analyses directed at dose response in this study by the sponsor. First, the overall data was compared between dosing arms. Second, because many events in the 50 mg arm occurred while subjects were still on 30 mg (i.e., first 12 weeks), an analysis comparing

the pre- and post titration period in those in the 50 mg arm was undertaken. Finally, the treatment arms were compared in the post-titration period (Weeks 12-52). The totality of these assessments was necessary to complete the dose response assessment.
There was an increase in the proportion of patients with injection site reactions, sinusitis and pain in extremity with dose. The density of these adverse events (AEs) also increased with increasing dose. However for these AEs the density is lower in the post titration phase compared to the pre-titration phase. Thus, no clear dose-response relationship for adverse events could be identified in study GLP112756. Please refer to section 2.3.3 for further details on exposure-response relationship for safety.

Intrinsic Factors

- **Renal Impairment:** Based on population pharmacokinetic analysis including a Phase 3 trial in patients with mild, moderate and severe renal impairment, exposures of albiglutide were increased by approximately 30 to 40% in severe renal impairment compared to those observed in type 2 diabetic patients with normal renal function. No dose adjustment is recommended in patients with renal impairment, which is supported by a dedicated safety and efficacy phase 3 study in patients with mild, moderate, and severe renally impaired patients. However, there is limited long term clinical experience in patients with severe renal impairment (only 19 subjects in Phase 3 program) and these patients experienced a relatively higher frequency of gastrointestinal events in the Phase 3 trial, therefore we recommend albiglutide to be used with caution in this patient population. Please see section 2.3.5 for further details.

- **Hepatic Impairment:** No formal studies of albiglutide have been performed in patients with hepatic impairment. Therapeutic proteins such as albiglutide are metabolized by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of albiglutide.

- **Age, Gender, Race and Body Weight:** Based on the population pharmacokinetic analysis with data collected from 1113 subjects, age, gender, race, and body weight had no clinically relevant effect on the pharmacokinetics of albiglutide.

Extrinsic Factors:

- **Gastric Emptying Effect:** There was a significant increase in the gastric emptying time ($t_{½}$) for both solid and liquid meals, following singe 100 mg sc dose of albiglutide. Note that the higher 100 mg dose was chosen to mimic the probable steady-state concentrations. For solid meal, the gastric emptying $t_{½}$ increased from 1.14 hours at baseline to 2.23 hours following albiglutide dosing. For liquids, gastric emptying $t_{½}$ increased from 0.28 hours at baseline to 0.69 hours following albiglutide dosing. Although increase in gastric emptying time was seen following single sc dose of albiglutide, no clinically relevant drug-drug interaction was seen following

multiple dose administration of albiglutide on the pharmacokinetics of warfarin, digoxin, simvastatin and oral contraceptives.

Drug-Drug Interactions: No clinically relevant drug-drug interaction was seen following multiple dose administration of albiglutide on the pharmacokinetics of warfarin, digoxin and oral contraceptives (Figure 1). Co-administration of albiglutide with simvastatin resulted in approximately 2 fold increase peak plasma concentrations of active metabolite simvastatin acid. Since the clinical relevance of this change is not known, OCP proposes to use caution when initiating albiglutide in patients who are on simvastatin dose of 20 mg or greater.

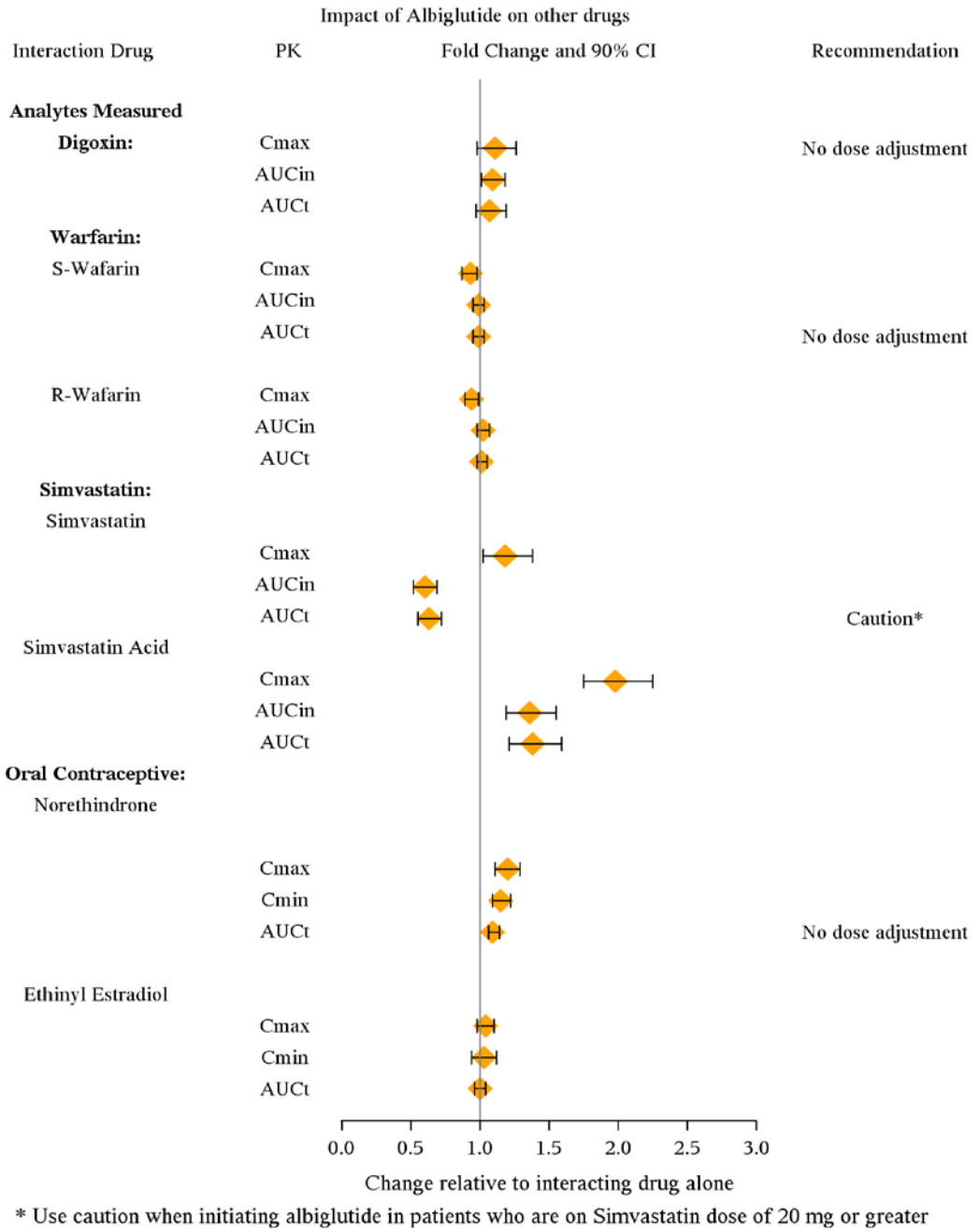


Figure 1: Effect of Albiglutide on the Pharmacokinetics of Co-Administered Drugs

- **Injection Site:** Albiglutide exposures were comparable following a single dose of 16 mg or 64 mg of albiglutide administered by sc injection(s) to one of three different sites (upper arm, thigh or abdomen) in subjects with T2DM (Figure 2).

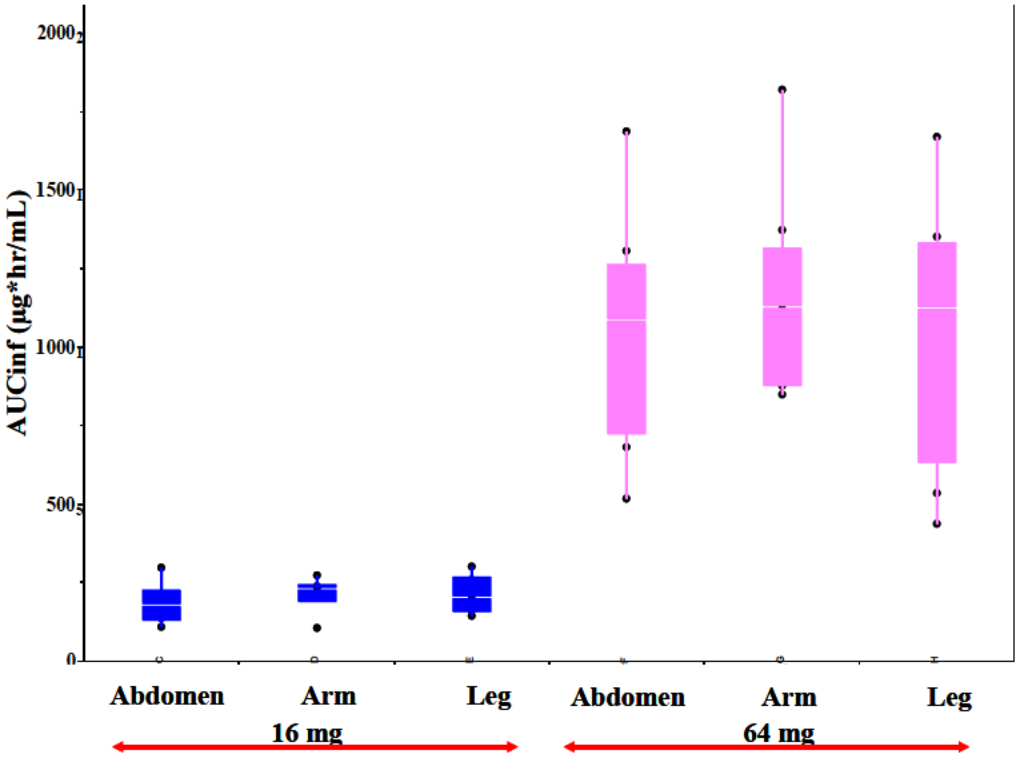


Figure 2: Exposure of Albiglutide Following Single SC Dose of 16 mg and 64 mg in Abdomen, Arm, and Leg

- **Pivotal BE Studies :** In this application all the Phase III studies used drug substance manufactured using Process 2 whereas the proposed commercial formulation utilizes drug substance manufactured using Process 3. Therefore, to bridge the drug substance manufactured through Process 2 to Process 3 sponsor conducted a single dose bioequivalence study. Sponsor also conducted a 12 week multiple dose safety and tolerability study utilizing the drug substances from Process 2 and Process 3.

  Statistical analysis demonstrated that there was no statistically significant difference in the AUC and C_{max} of albiglutide between Process 3 and Process 2 and the two products are bioequivalent after a single sc dose of 30 mg albiglutide (Figure 3). The 90% confidence intervals of the ratios of the least square means for AUC_{inf} and C_{max} are within the criterion interval of 0.80 to 1.25.

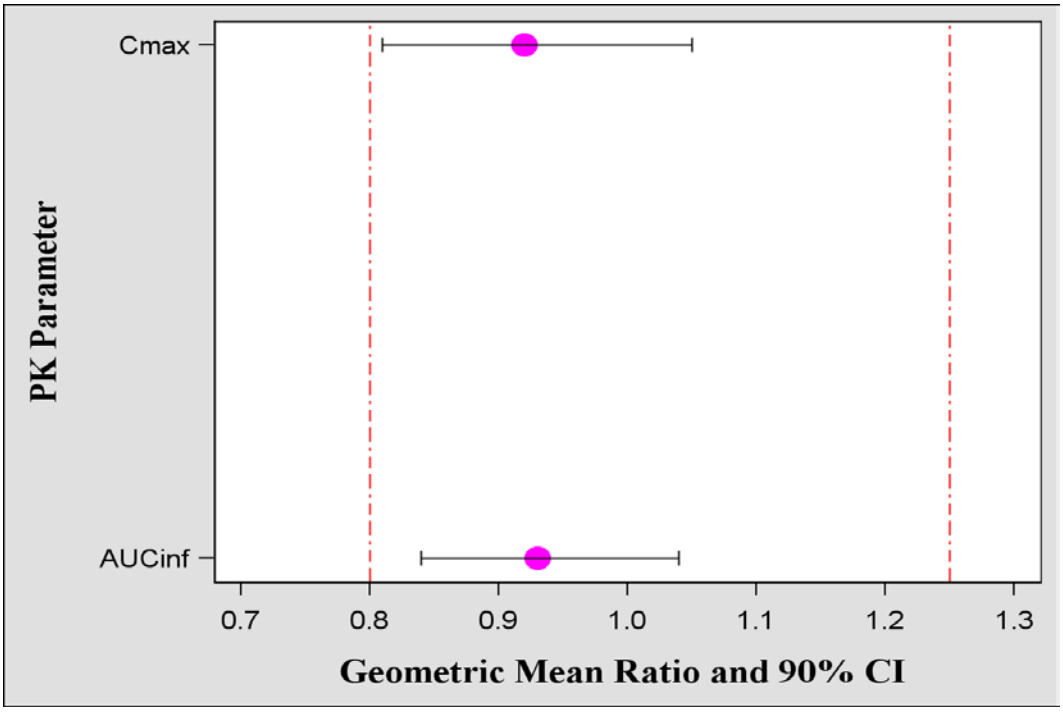


Figure 3: Statistical Analysis of Pharmacokinetic Parameters of Albiglutide following Single Dose Administration of Albiglutide from Process 2 and Process 3: BE Phase

2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

General attributes of albiglutide and the proposed drug product are summarized above under executive summary. In brief, Albiglutide is an agonist of the GLP-1 receptor and has been developed by GSK for the treatment of adult T2DM patients, as an adjunct to diet and exercise or [redacted] (b) (4) to improve glycemic control.

Sponsor's proposed dosing recommendation for albiglutide is 30 mg once weekly sc dose to be administered in the abdomen, thigh, or upper arm region. If the 30 mg dose does not result in acceptable glycemic control, sponsor proposed that the dose can be increased to 50 mg weekly injection.

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Albiglutide is an agonist of the GLP-1 receptor. Several drugs in this class have been approved (exenatide, liraglutide) or are under review by Agency. Albiglutide is a long acting GLP-1 agonist with once weekly dosing.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Albiglutide is a recombinant fusion protein consisting of two copies of a 30-amino acid sequence of modified human glucagon-like peptide 1 (GLP-1, fragment 7-36) genetically linked in series to human albumin (hA). Specifically, the first modified GLP-1 copy is fused at its [redacted] (b) (4) of the second copy. This peptide, in turn, is genetically fused at its [redacted] (b) (4) of hA. A schematic representation of albiglutide is shown in Figure 4 and a structural model is shown in Figure 5.

The GLP-1 sequence has been modified with a glycine substituted for the naturally occurring alanine at position 8 (highlighted in blue in Figure 4) in order to confer resistance to dipeptidylpeptidase IV (DPP-IV) mediated proteolysis. The predicted molecular mass of albiglutide as calculated from amino acid sequence is 72971.4 Da.

Figure 4: Schematic Representation of Albiglutide

Source: Sponsor's report of Quality Overall Summary, Pg5

Figure 5: Albiglutide Structural Model

Source: Sponsor's report of Quality Overall Summary, Pg5

Drug Product and Formulation:
Commercial albiglutide drug product is supplied as a single-use, sterile lyophilized cake in a clear glass dual chamber cartridge (DCC) to deliver either 30 mg or 50 mg of albiglutide in a 0.5 mL injection volume.

The DCC enables the lyophilized drug product and diluents to be held in a single container. The front chamber contains albiglutide in a lyophilized cake. The front

chamber of the DCC is sealed with a plastic snap-on cap encasing a (b) (4) rubber closure disc. The rear chamber of the DCC contains diluents for reconstitution. The rear chamber is filled with Water for Injection (WFI) and is also sealed with a (b) (4) rubber stopper. The contents of the two chambers of the DCC are separated by a (b) (4) rubber stopper. The external appearance of the albiglutide for injection DCC is shown in Figure 6.

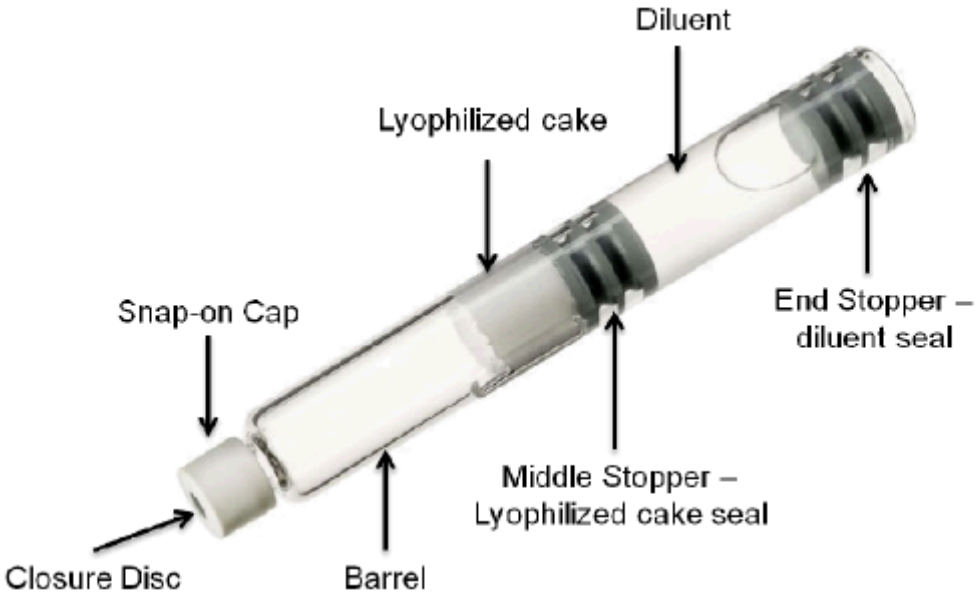


Figure 6: Appearance of the Dual Chamber Cartridge (DCC)

Source: Sponsor's report of Description and Composition of Drug Product, Pg1

Each DCC of albiglutide for injection, 30 mg/DCC or 50 mg/DCC, contains either 40.30 mg or 66.95 mg of sterile lyophilized albiglutide, respectively. The content has been optimized to ensure a 30 mg or a 50 mg dose is delivered. Before injection, the lyophilized cake is reconstituted with 0.65 mL of diluent. The overfill in the DCC is intended to ensure the specified amount of albiglutide is delivered in a 0.5 mL injection volume. The composition of the albiglutide for injection, 30 mg/DCC and 50 mg/DCC formulas are presented in Table 1.

Table 1: Composition of Albiglutide for Injection to be Marketed Product (30 mg/DCC and 50 mg/DCC)

Component	Quantity (mg)		Function	Reference to Standards
	30 mg/DCC	50 mg/DCC		
Albiglutide	40.30	66.95	(b) (4)	GSK Specification
Trehalose dihydrate	(b) (4)			USP-NF, EP
Mannitol				USP-NF, EP, JP
(b) (4)				USP-NF, EP
Sodium phosphate (b) (4)				USP-NF
Polysorbate 80				USP-NF, EP, JP
Water For Injection	0.65 mL	0.65 mL		USP-NF, EP, JP

Source: Sponsor's report of Description and Composition of Drug Product, Pg3

2.1.3 What is the mechanism of action and therapeutic indication?

GLP-1 is an incretin secreted by intestinal L-cells in response to ingestion of food and regulates postprandial blood glucose concentrations by stimulating glucose-dependent insulin secretion by the pancreas resulting in increased glucose utilization by tissues. Albiglutide may also reduce hepatic glucose output by inhibiting glucagon release and prolonging the gastric emptying time which delays food absorption and decreases the glucose absorption rate.

In preclinical studies, albiglutide was found to be less potent than native GLP-1 at GLP-1Rs. Albiglutide was 9.7- to 15.1-fold less potent than GLP-1 at the human GLP-1R and 10.2-fold less potent than GLP-1 at the cynomolgus monkey GLP-1R. Please refer to Pharmacology and Toxicology review by Dr. Ron Wange for further details on in-vitro and non clinical potency of albiglutide.

2.1.4 What are the proposed dosage and route of administration?

Albiglutide is supplied as single use prefilled pen providing 30 mg or 50 mg albiglutide. The drug product is intended for once weekly sc injection indicated to improve glycemic control in patient with diabetes mellitus.

Proposed Dosage and Administration:

- Administer TRADENAME 30 mg weekly as a sc injection in the abdomen, thigh, or upper arm region. The dose may be increased to 50 mg weekly based on individual glycemic response.
- TRADENAME may be administered at any time of day without regard to meals. Administer TRADENAME once a week on the same day each week. The day of weekly administration may be changed if necessary as long as the last dose was administered 4 or more days before.
- If a dose is missed, it should be administered as soon as possible within 3 days after the missed dose. Thereafter, patients can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, patients should wait until their next regularly scheduled weekly dose.
- When initiating albiglutide, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.

2.1.5 Is any OSI (Office of Scientific Investigation) inspection requested for any of the clinical studies?

Yes. Sponsor used drug substance from Process 2 in most of their Phase 1, Phase 2 and Phase 3 Studies. The proposed to-be-marketed formulation contains drug substance from Process 3. To bridge the Process 2 drug substance to Process 3 drug substance sponsor conducted a single dose BE study and a multiple dose safety and efficacy study of 12 weeks (Study GLP114856) to bridge the drug substance from Process 2 and Process 3. From a Clinical Pharmacology standpoint, an OSI inspection is requested for the single dose BE study. The results of the OSI inspection were pending at the time of review.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Albiglutide for the treatment of T2DM has been evaluated in a comprehensive global program of studies including 10 Phase I studies, 5 Phase II studies (and 1 study in non-diabetic patients with congestive heart failure), and 8 Phase III studies involving approximately 7500 patient-years of overall program exposure at the time of this application (and 10,000 patient-years of overall program exposure at the close of the ongoing 3 year Phase III studies).

Efficacy and Safety Program (Phase 2b/3 Program): Phase 2 program consists of 5 studies (Figure 7). Three Phase II studies (1 global study [GLP110125] and 2 studies in Japan [GLP 110932, GLP107856]) have been conducted to explore the dose range and frequency of administration for albiglutide. A fourth Phase II study evaluated the effects of albiglutide on counter-regulatory hormone response and recovery from hypoglycaemia in T2DM subjects (GLP108372). The fifth Phase II study (GLP114856) was conducted to evaluate bioequivalence after a single 30 mg dose of Process 2 (Phase III material) and Process 3 (commercial material) albiglutide

Phase 3 program supporting the efficacy and safety of albiglutide includes 8 well-controlled Phase III studies in patients with T2DM. At the time of this submission, five of these Phase III studies (156-week studies) were ongoing (GLP112753, GLP112754, GLP112755, GLP112756 and GLP112757). The patient population enrolled in the albiglutide program spanned newly diagnosed subjects treated with diet and exercise alone through to subjects on background oral monotherapy, oral dual therapy, oral triple therapy and insulin. The Phase III program also included a study that evaluated the efficacy and safety of albiglutide in combination with basal insulin (insulin glargine).

The Phase 3 studies in albiglutide program were designed to demonstrate efficacy both the short and long term (up to 3 years, with data for 2 years of treatment included in this submission), to assess the durability of glycemic control, and to evaluate long-term safety and tolerability, including cardiovascular (CV) safety. The primary efficacy endpoint for all of the albiglutide Phase III studies was change in HbA1c from baseline. Secondary endpoints included change in FPG and body weight from baseline, the proportion of subjects requiring hyperglycemia rescue, and the proportion of subjects achieving HbA1c treatment goals.

Baseline HbA1c values in the albiglutide group ranged from 8.05% to 8.47%. Treatment with albiglutide consistently led to improvements in glycemic control irrespective of whether albiglutide was administered as monotherapy or in combination with MET, SUs, TZDs or basal insulin; the mean reduction from Baseline HbA1c at the time of the primary endpoint (26 weeks to 104 weeks ranged between -0.6% to -0.9%).

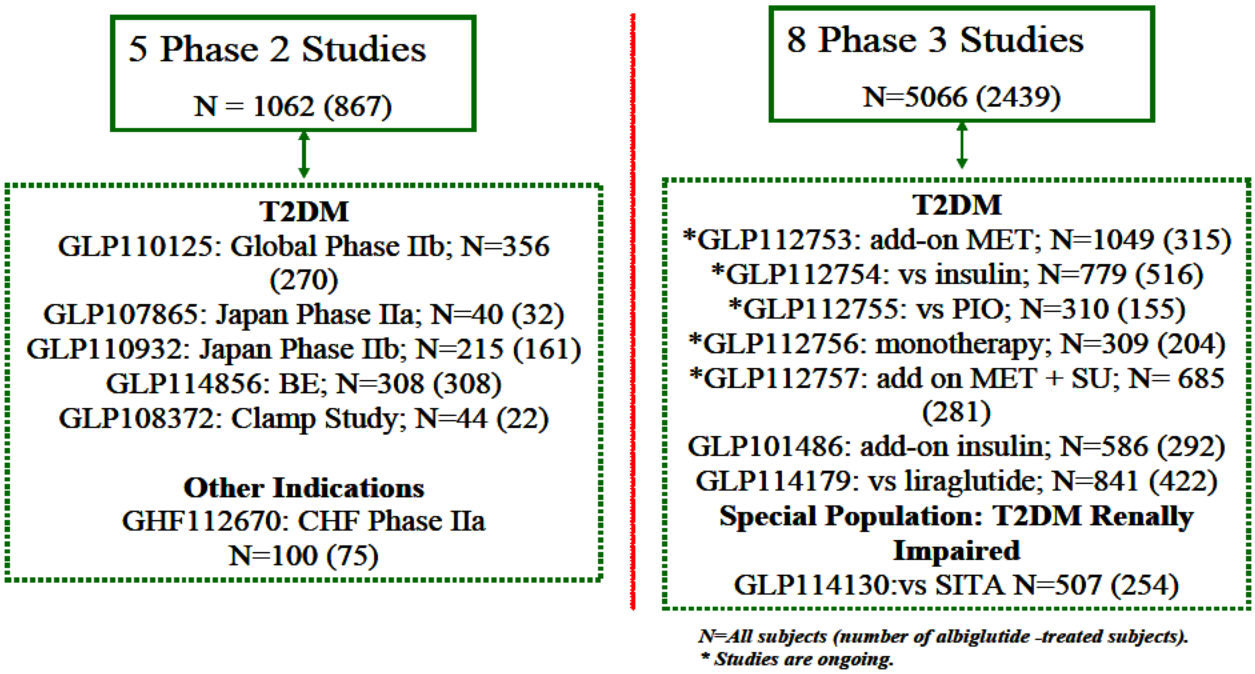


Figure 7: Overview of Albiglutide Clinical Development Program

Clinical Pharmacology Program: The clinical pharmacology program for albiglutide includes 10 Phase 1 studies (Figure 8). In general, clinical pharmacology program for albiglutide consists of Phase I studies to investigate the PK and PD of albiglutide in both healthy volunteers and subjects with T2DM. A single and repeat dose studies, a PD study to evaluate the impact of albiglutide on gastric emptying of both solids and liquids, a relative bioavailability study of single doses of albiglutide administered subcutaneously to 1 of 3 different sites (arm, leg or abdomen), drug interaction studies, a tQT safety study and a PK study in subjects with varying degrees of renal function. Figure 8 summarizes the list of key clinical pharmacology trials in albiglutide program.

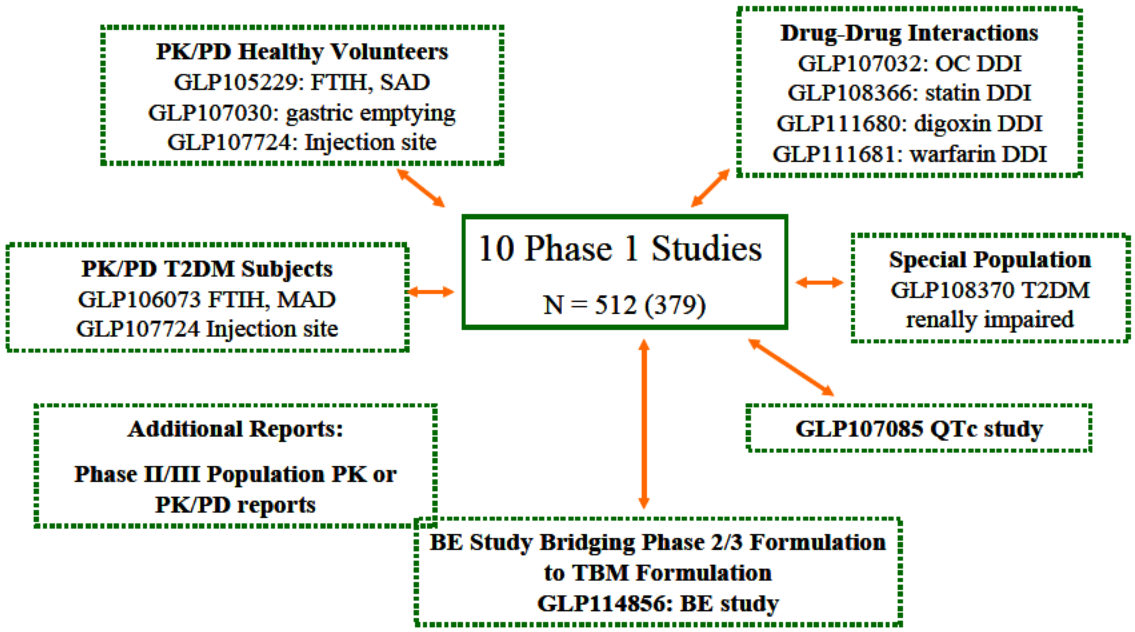


Figure 8: Overview of Albiglutide Clinical Pharmacology Program

2.2.2 *What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?*

The American Diabetes Association (ADA) recommends the use of glycosylated hemoglobin A1c (HbA1c) levels as an indicator of glycemic control. The primary objective in all of the therapeutic confirmatory trials was to confirm the efficacy of albiglutide in controlling glycemia as measured by change from baseline in HbA1c after treatment in subjects with T2DM. This was done by comparing the difference in change of HbA1c from baseline to end-of-treatment between albiglutide and placebo or active comparator. In addition, to other glycemic parameters, PD parameter based on the mechanism of action of drug (such as fasting plasma glucose, self-measured plasma glucose) was measured in some clinical studies.

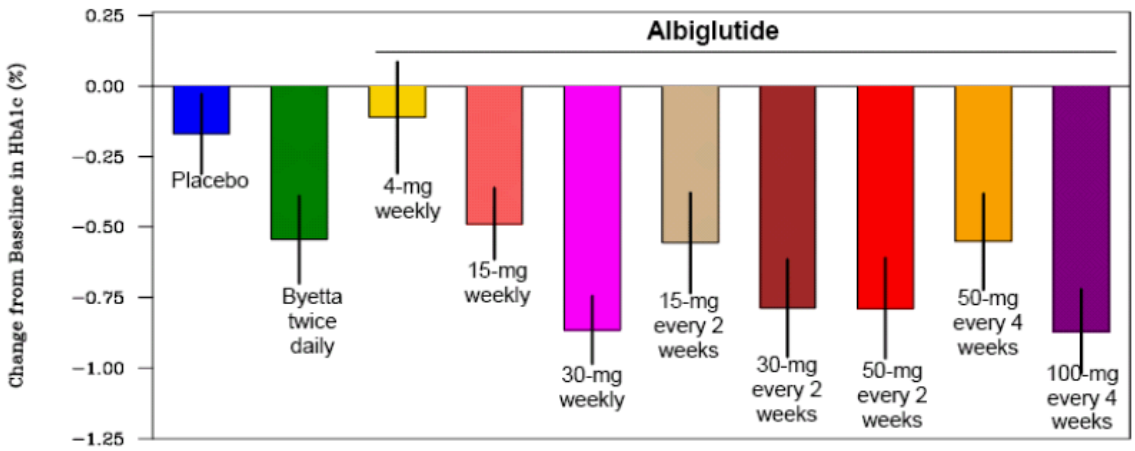
2.2.3 *Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Yes. Please refer to the analytical section (2.8) for details.

2.3 Exposure-Response

2.3.1 What was the rationale for Dose Selection in Phase 3 Program?

The selection of albiglutide 30 mg weekly as a starting dose in Phase III was determined based on PK/PD data from Phase 1 studies and efficacy data from the Phase IIB Study GLP110125. In the GLP110125 study, albiglutide was administered once weekly (4 mg, 15 mg, 30 mg), every other week (15 mg, 30 mg, 50 mg), or every 4 weeks (50 mg, 100 mg) for 16 weeks. The HbA1c reduction from baseline at Week 16, across all the treatment groups, in Study GLP110125 is shown in Figure 9. The treatment difference for albiglutide 30 mg weekly versus placebo was statistically significant (-0.62%, p=0.0027). According to sponsor's analysis from a benefit-risk perspective, initial dosing with 30 mg albiglutide weekly achieved optimal glycemic control. Phase 2 data suggested that albiglutide doses above 50 mg may be associated with an increase in gastrointestinal adverse events (e.g., nausea and vomiting). The 50 mg weekly dosing regimen was not studied in the Phase IIb dose ranging studies in T2DM subjects. However, higher doses were tested in the Phase IIb study GLP110125 with an every other week (50 mg) or every 4 week (50 mg and 100 mg) dosing interval. Since there was some increase in efficacy as the dose increased within the regimens tested (Figure 9), it was postulated that up titrating to 50 mg from 30 mg in the Phase III studies would provide better efficacy without compromising gastrointestinal tolerability.



Data Source: Figure 14.2-1.14

Figure 9: Mean (±SE) Change From Baseline in HbA1c at Week 16(Intent-to-Treat Population –LOCF) in Study GLP110125.

Source: Sponsor report on Clinical Overview

2.3.2 *Is there dose-response for effectiveness endpoints?*

Yes, there is evidence of dose-response relationship for mean change from baseline in HbA1c in type 2 diabetes patients in study GLP112756. Patients were randomized to either receive albiglutide 30 mg without up titration or to receive albiglutide 30 mg followed by up titration to 50 mg at week 12 (forced titration). The time-profiles for the mean change from baseline in HbA1c in GLP112756 are shown in Figure 10. There is a larger decline in HbA1c with increased dose of 50 mg weekly compared to 30 mg weekly. GLP112756 is the only Phase 3 trial that provides information regarding the dose-response relationship of albiglutide. In other Phase 3 trials uptitration from 30 mg to 50 mg albiglutide occurred because of insufficient glycemic control with albiglutide 30 mg (optional uptitration following a protocol-specific algorithm).

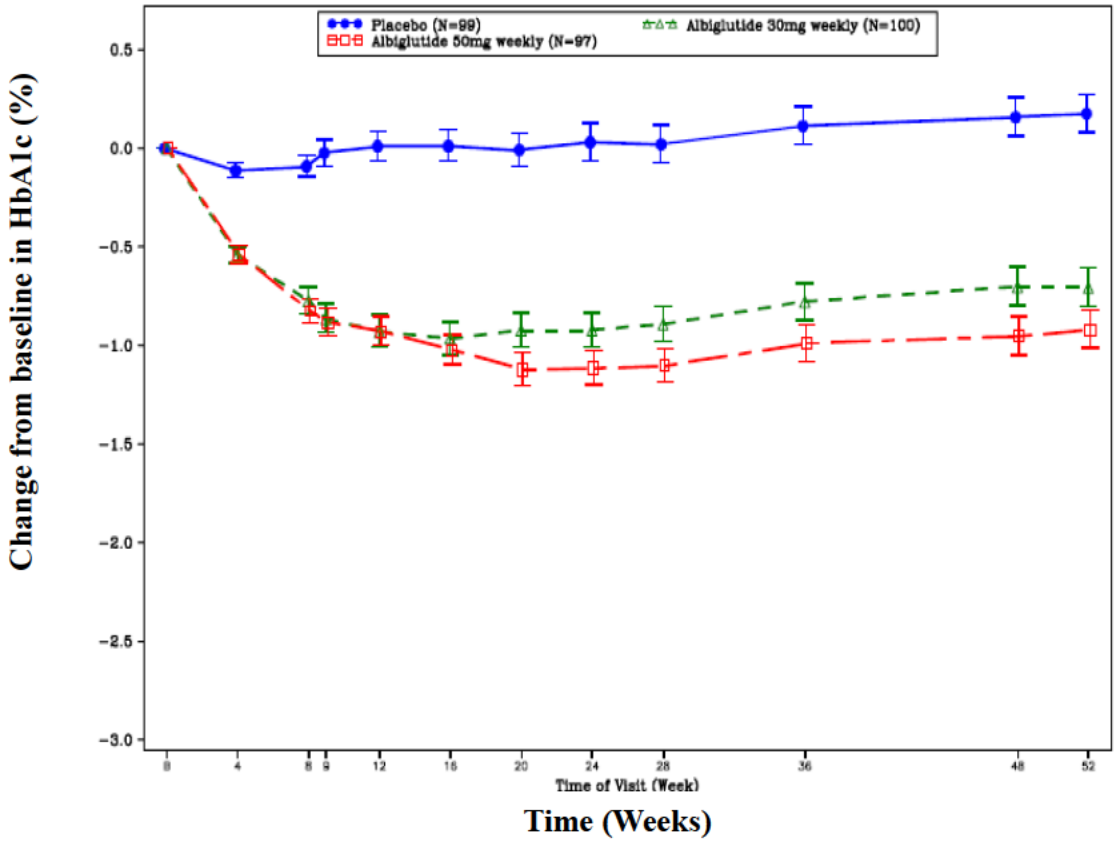


Figure 10: Time profiles for mean change from baseline in HbA1c in GLP 112756 upon administration of placebo (blue), 30 mg weekly (green) and 50 mg weekly (red) doses of albiglutide. Source:

Source Figure 3 of sponsor's study report.

2.3.3 *Is there dose-response for safety endpoints?*

Study GLP112756 suggested no clear dose response relationship for safety endpoints. Since GLP112756 had a forced titration design, there are three analyses directed at dose response in this study by the sponsor. First, the overall data was compared between dosing arms. Second, because many events in the 50 mg arm occurred while subjects

were still on 30 mg (i.e. first 12 weeks), an analysis comparing the pre- and post titration period in those in the 50 mg arm was undertaken. Finally, the treatment arms were compared in the post-titration period (Weeks 12-52). The totality of these assessments was necessary to complete the dose response assessment.

There was an increase in the proportion of patients with injection site reactions, sinusitis and pain in extremity with dose. The density of these adverse events (AEs) also increased with increasing dose (Table 2). However for these AEs the density is lower in the post titration phase compared to the pre-titration phase (Table 3). Thus no clear dose-response relationship for adverse events could be identified in GLP112756.

In the phase 3 trials where optional uptitatraion was employed (Studies GLP108486, GLP112753, GLP112754, and GLP112757), among common AEs (sinusitis, nausea, vomiting, back pain, cough, diabetic retinopathy and hypertension) all had higher proportion and AE incidence in the 50 mg overall group compared to 30 mg group. However, with the exception of diabetic retinopathy, the proportion and AE densities for those AEs were lower post-titration than pre-titration (data not shown). The pre-titration event rate for diabetic retinopathy was 1.62 AEs/100 person years, while the post-titration rate was 3.27 AEs/100 person years. For injection site reactions, there was a lower proportion of subjects and AE density in 50 mg (14.3%, 54.66/100 person years) compared to the 30 mg (15.9%. 56.92/100 person years). Within the 50 mg arm, the proportion of subjects having an injection site reaction and the event density was lower in the post titration period (8.2%, 44.48/100 person years) compared to the pre-titration period (8.8%, 77.60/100 person years). This supports the conclusion from the GLP112756 study that there is not a clinically relevant dose response with regard to injection site reaction.

Table 2: On Therapy Adverse Events by Treatment Arms in GLP 112756

	Placebo (N=101)		Albiglutide 30 mg weekly (N=101)		Albiglutide 50 mg weekly (N=99)	
	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]
Any on-therapy event	82 (81.2)	569/284.26	85 (84.2)	644/294.26	86 (86.9)	535/279.88
Infections and Infestations						
Any Event	55 (54.5)	104/51.96	53 (52.5)	95/43.41	47 (47.5)	112/58.59
Upper respiratory tract infection	16 (15.8)	22/10.99	11 (10.9)	12/5.48	16 (16.2)	19/9.94
Nasopharyngitis	6 (5.9)	9/4.50	8 (7.9)	11/5.03	7 (7.1)	8/4.19
Bronchitis	8 (7.9)	11/5.50	7 (6.9)	8/3.66	7 (7.1)	8/4.19
Sinusitis	6 (5.9)	7/3.50	6 (5.9)	6/2.74	7 (7.1)	10/5.23
Influenza	3 (3.0)	3/1.50	7 (6.9)	11/5.03	5 (5.1)	6/3.14
Urinary tract infection	6 (5.9)	11/5.50	2 (2.0)	2/0.91	7 (7.1)	11/5.75
Cellulitis	2 (2.0)	2/1.00	7 (6.9)	7/3.20	2 (2.0)	3/1.57

	Placebo (N=101)		Albiglutide 30 mg weekly (N=101)		Albiglutide 50 mg weekly (N=99)	
	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]
Pharyngitis	6 (5.9)	9/4.50	3 (3.0)	4/1.83	3 (3.0)	6/3.14
Gastrointestinal disorders						
Any event	36 (35.6)	70/34.97	41 (40.6)	77/35.18	34 (34.3)	68/35.57
Diarrhoea	15 (14.9)	20/9.99	12 (11.9)	19/8.68	15 (15.2)	19/9.94
Nausea	10 (9.9)	10/5.00	14 (13.9)	16/7.31	10 (10.1)	16/8.37
Gastroesophageal reflux disease	2 (2.0)	4/2.00	2 (2.0)	2/0.91	5 (5.1)	5/2.62
Abdominal pain	8 (7.9)	8/4.00	4 (4.0)	4/1.83	2 (2.0)	2/1.05
Dyspepsia	6 (5.9)	6/3.00	4 (4.0)	5/2.28	2 (2.0)	2/1.05
General disorders and administration site conditions						
Any event	22 (21.8)	68/33.97	32 (31.7)	121/55.29	37 (37.4)	115/60.16
Injection site reaction	2 (2.0)	30/14.99	10 (9.9)	42/19.19	18 (18.2)	71/37.14
Fatigue	5 (5.0)	6/3.00	7 (6.9)	7/3.20	4 (4.0)	4/2.09
Chest Pain	5 (5.0)	6/3.00	5 (5.0)	5/2.28	1 (1.0)	1/0.52
Injection site haematoma	5 (5.0)	11/5.50	1 (1.0)	1/0.46	2 (2.0)	2/1.05
Musculoskeletal and connective tissue disorders						
Any event	29 (28.7)	52/25.98	34 (33.7)	66/30.16	24 (24.2)	40/20.93
Back pain	6 (5.9)	7/3.50	8 (7.9)	8/3.66	5 (5.1)	5/2.62
Pain in extremity	3 (3.0)	3/1.50	6 (5.9)	6/2.74	7 (7.1)	7/3.66
Arthralgia	6 (5.9)	9/4.50	6 (5.9)	11/5.03	4 (4.0)	9/4.71

Table 3: On therapy Adverse Events Occurring in Treated Subjects in the Up titration Group Before and After Titration in GLP112756

	Albiglutide 50 mg weekly (N=99)			
	Before Titration[1]		After Titration[1]	
	n (%)	Number of AEs/Density[2]	n (%)	Number of AEs/Density[2]
Any ontherapy event	53 (53.5)	121/488.62	73 (73.7)	414/248.81
Infections and Infestations				
Any Event	17 (17.2)	22/88.84	41 (41.4)	90/54.09
Upper respiratory tract infection	2 (2.0)	3/12.11	14 (14.1)	16/9.62
Nasopharyngitis	1 (1.0)	1/4.04	6 (6.1)	7/4.21
Bronchitis	0	0	7 (7.1)	8/4.81
Sinusitis	2 (2.0)	2/8.08	6 (6.1)	8/4.81
Urinary tract infection	2 (2.0)	3/12.11	6 (6.1)	8/4.81
Gastrointestinal disorders				
Any event	14 (14.1)	20/80.76	28 (28.3)	48/28.85
Diarrhoea	7 (7.1)	7/28.27	10 (10.1)	12/7.21
Nausea	4 (4.0)	4/16.15	8 (8.1)	12/7.21
General disorders and administration site conditions				
Any event	12 (12.1)	20/80.76	27 (27.3)	95/57.09
Injection site reaction	3 (3.0)	10/40.38	15 (15.2)	61/36.66
Musculoskeletal and connective tissue disorders				
Any event	6 (6.1)	10/40.38	19 (19.2)	30/18.03
Back pain	1 (1.0)	1/4.04	4 (4.0)	4/2.40
Pain in extremity	1 (1.0)	1/4.04	6 (6.1)	6/3.61
Nervous system disorders				
Any event	5 (5.1)	5/20.19	17 (17.2)	25/15.02
Headache	2 (2.0)	2/8.08	7 (7.1)	11/6.61
Respiratory, thoracic, and mediastinal disorders				
Any event	5 (5.1)	5/20.19	12 (12.1)	20/12.02
Cough	1 (1.0)	1/4.04	6 (6.1)	7/4.21
Vascular disorders				
Any event	2 (2.0)	2/8.08	11 (11.1)	11/6.61
Hypertension	1 (1.0)	1/4.04	8 (8.1)	8/4.81

2.3.4 *Is the proposed dosing scheme of 30 mg once weekly with uptitration to 50 mg weekly based on individual glycemic response reasonable?*

The proposed dose appears reasonable because:

- There is an increase in mean change from baseline in HbA1c in 50 mg dose group compared to 30 mg dose group in forced titration study GLP 112756 (Figure 10)
- There is no clear dose response relationship for safety endpoints identified in GLP 112756 (see Pharmacometrics review Appendix 4.3).
- There was improvement in response (HbA1c) in patients after dose titration in optional up-titration studies. Figure 11 shows mean change from baseline in HbA1c for subjects requiring uptitration of albiglutide in each of the 4 studies which allowed optional uptitration. The data for each of the 4 studies show an initial rapid drop in HbA1c. For these subjects, however, there was a return of hyperglycemia which resulted in the uptitration of their albiglutide dose from 30 mg weekly to 50 mg weekly. The vertical dashed line indicates the last HbA1c value along the relative time scale prior to uptitration of the dose. The data after this uptitration line indicate a restoration of HbA1c to levels seen with the initial 30-mg dose regimen.

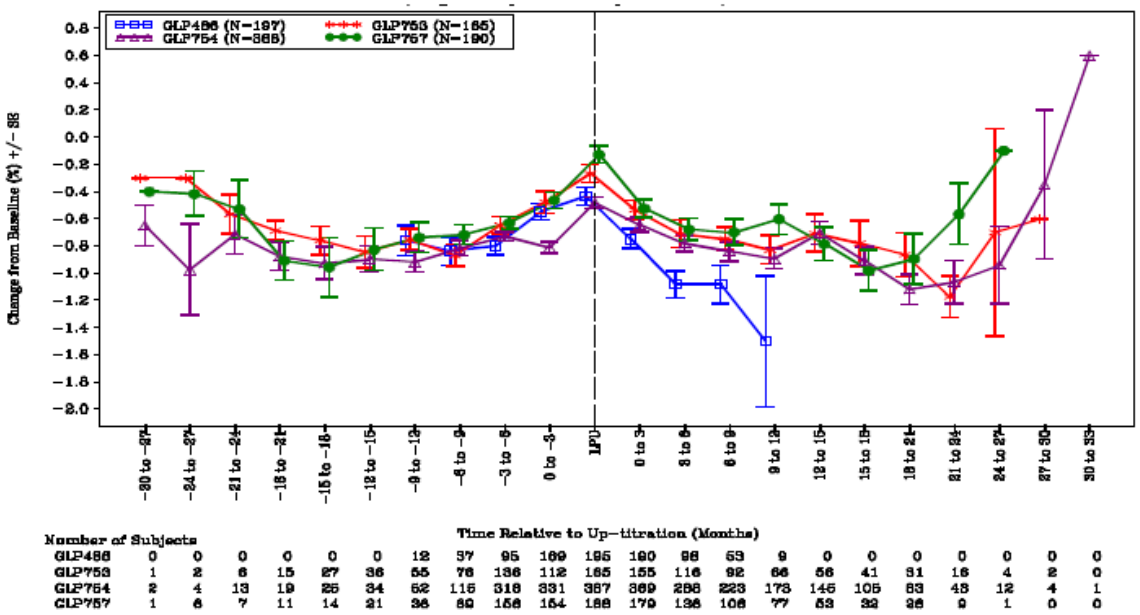


Figure 11: Mean change from baseline in HbA1c (%) relative to time of uptitration excluding post rescue values.

Source: Figure 21 of Sponsor's Summary of Clinical Efficacy.

2.3.5 *Is there any need for dose adjustment in patients with renal impairment based on the safety and efficacy analysis in renally impaired patients?*

No dose adjustment is needed in patients with renal impairment. However, caution is recommended when using albiglutide in patients with severe renal impairment.

Efficacy in Renally Impaired Patients:

In this application, sponsor conducted a Phase 3 trial in patients with mild (n=128), moderate (n=102) and severe (n=19) renal impairment (Study # GLP114130). The primary objective of this study was to evaluate the efficacy of albiglutide as compared with sitagliptin on the glycosylated hemoglobin (HbA1c) change from baseline at week 26.

Renally impaired subjects with T2DM whose glycemia was inadequately controlled on their current regimen of diet and exercise or their antidiabetic therapy regimen of metformin, TZD, SU, or any combination of these OAD medications were recruited into the study. Approximately 500 subjects were planned to be randomly assigned to one of the following 2 treatment groups in a 1:1 ratio such that

- Approximately 250 subjects were assigned to albiglutide (30 mg weekly with uptitration, if needed, to 50 mg weekly) + sitagliptin matching placebo
- Approximately 250 subjects were assigned to albiglutide matching placebo + sitagliptin

Summary statistics for change from baseline in HbA1c by renal impairment through week 26 are presented in Table 4. The mean decrease in HbA1c from baseline was –0.72% for mild renal impaired patients, –0.88% for moderate renally impaired patients and –1.08% for severe renal impaired subjects. Thus, it can be concluded that the efficacy of albiglutide in not affected with renal impairment.

Table 4: Analysis of Change From Baseline in HbA1c (%) at Week 26 by Renal Impairment Severity (ITT Population – LOCF)

	Albiglutide (N=246)			Sitagliptin (N=240)		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Number of subjects[1]	125	98	19	122	99	15
Number (%) of values carried forward	17 (13.6)	21 (21.4)	2 (10.5)	15 (12.3)	37 (37.4)	6 (40.0)
Baseline – mean (SD)	7.96 (0.804)	8.26 (0.922)	8.05 (0.746)	8.16 (0.894)	8.28 (0.927)	8.32 (0.922)
Week 26 – mean (SD)	7.23 (0.887)	7.37 (1.144)	6.97 (1.103)	7.50 (1.066)	7.91 (1.413)	7.67 (1.261)
Change from Baseline – mean (SD)	-0.72 (0.807)	-0.88 (0.998)	-1.08 (0.914)	-0.66 (0.879)	-0.37 (1.325)	-0.65 (1.239)
Model-adjusted change from Baseline[2]						
LS mean (SE)	-0.80 (0.087)	-0.83 (0.097)	-1.08 (0.221)	-0.67 (0.087)	-0.31 (0.097)	-0.61 (0.249)
95% CI	(-0.97, -0.63)	(-1.03, -0.64)	(-1.52, -0.65)	(-0.84, -0.50)	(-0.50, -0.12)	(-1.10, -0.12)
Difference from sitagliptin[2]						
Difference of LS means	-0.13	-0.53	-0.47			
95% CI	(-0.37, 0.11)	(-0.80, -0.26)	(-1.12, 0.18)			

Source Data: Table 14.2-1.6.9.

CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.

Note: This analysis used the LOCF method for missing postbaseline HbA_{1c} values. The HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline HbA_{1c} + renal impairment + prior myocardial infarction history + age category + region + treatment*renal impairment. The difference of least squares means (albiglutide - sitagliptin) is from ANCOVA model. The p-value for the interaction term = 0.0855.

Source: Sponsor study report of trial GLP114130

Safety in Renally Impaired Patients: The overall event rate in the albiglutide group was higher for subjects with moderate and severe renal impairment than for subjects with mild renal impairment (Table 5)

Table 5: On-Therapy Related Adverse Events Occurring in at Least 2% of Subjects in Either Treatment Group Overall Presented by Renal Impairment Severity (Safety Population)

	Albiglutide n (%)						Sitagliptin n (%)					
System Organ Class Preferred Term	Mild (N=128)	Number of Events/ Rate[1]	Moderate (N=102)	Number of Events/ Rate[1]	Severe (N=19)	Number of Events/ Rate[1]	Mild (N=128)	Number of Events/ Rate[1]	Moderate (N=101)	Number of Events/ Rate[1]	Severe (N=17)	Number of Events/ Rate[1]
Any related AE	25 (19.5)	59 / 44.62	22 (21.6)	86 / 84.30	7 (36.8)	20 / 102.01	17 (13.3)	29 / 21.86	14 (13.9)	33 / 36.66	2 (11.8)	5 / 31.87
Gastrointestinal disorders												
Any related event	8 (6.3)	11 / 8.32	13 (12.7)	19 / 18.63	4 (21.1)	9 / 45.90	8 (6.3)	10 / 7.54	6 (5.9)	14 / 15.55	1 (5.9)	2 / 12.75
Diarrhoea	1 (0.8)	1 / 0.76	3 (2.9)	3 / 2.94	2 (10.5)	3 / 15.30	3 (2.3)	3 / 2.26	1 (1.0)	1 / 1.11	0	0
General disorders and administration site conditions												
Any related event	12 (9.4)	29 / 21.93	7 (6.9)	56 / 54.90	3 (15.8)	6 / 30.60	6 (4.7)	8 / 6.03	2 (2.0)	4 / 4.44	0	0
Injection site reaction	4 (3.1)	15 / 11.34	4 (3.9)	53 / 51.95	1 (5.3)	1 / 5.10	0	0	0	0	0	0
Injection site pruritus	3 (2.3)	4 / 3.03	1 (1.0)	1 / 0.98	1 (5.3)	1 / 5.10	0	0	0	0	0	0
Injection site haematoma	1 (0.8)	1 / 0.76	0	0	0	0	4 (3.1)	4 / 3.02	2 (2.0)	2 / 2.22	0	0
Nervous system disorders												
Any related event	4 (3.1)	4 / 3.03	2 (2.0)	2 / 1.96	0	0	2 (1.6)	2 / 1.51	2 (2.0)	7 / 7.78	1 (5.9)	1 / 6.37
Metabolism and nutrition disorders												
Any related event	3 (2.3)	4 / 3.03	3 (2.9)	3 / 2.94	1 (5.3)	1 / 5.10	2 (1.6)	2 / 1.51	1 (1.0)	1 / 1.11	0	0
Skin and subcutaneous tissue disorders												
Any related event	3 (2.3)	4 / 3.03	1 (1.0)	1 / 0.98	1 (5.3)	1 / 5.10	1 (0.8)	2 / 1.51	0	0	0	0
Renal and urinary disorders												
Any related event	1 (0.8)	1 / 0.76	2 (2.0)	3 / 2.94	1 (5.3)	1 / 5.10	0	0	3 (3.0)	5 / 5.55	2 (11.8)	2 / 12.75
Renal failure	1 (0.8)	1 / 0.76	1 (1.0)	2 / 1.96	0	0	0	0	3 (3.0)	4 / 4.44	2 (11.8)	2 / 12.75

Source Data: Table 14.3.1-1.2.1.1.

Note: On-therapy adverse events (AEs) were those that had a start date on or after the first day of study medication and within 56 days after the end of study medication. Adverse events that were missing an investigator-assigned relationship to study medication were considered related and included in this summary. For each level of summarization, a subject was counted once if the subject reported 1 or more events. Percentages were based on the number of subjects in each treatment group within each subgroup. The system organ class and preferred term within the system organ class are presented by decreasing frequency of the incidence for both treatment groups combined.

1. Number of AEs = the total number of AEs at each level of summarization. Rate per 100 person-years = 100 * (number of AEs divided by person-years), where person-years was defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group within each subgroup during the treatment period being summarized.

Source: Sponsor study report of trial GLP114130

Reviewers Comment: Efficacy was not affect by the renal function. However, in terms of safety severe renal impairment (eGFR ≥15 to < 30 ml/min) receiving albiglutide experienced a higher frequency of gastrointestinal events of nausea, diarrhea and vomiting compared to subjects with mild and moderate renal impairment. Most of the GI event occurs early on in the treatment where most of the patients were not escalated to the dose of 50 mg albiglutide. In addition these events were noted as mild events and were resolved with in 2-3 days of occurrence.

Since GI related events may worsen renal function, caution is recommended when initiating or escalating doses of albiglutide in patients with severe renal impairment. In addition only 19 subjects with severe renal impairment was enrolled in the trial and there is a limited long term clinical experience in patients with severe renal impairment.

2.4 What are the PK characteristics of the drug?

2.4.1 What are the single and multiple dose PK characteristic of albiglutide in healthy and in T2DM adult subjects?

Phase 1 PK/PD studies in healthy and T2DM subjects only used single dose administration of albiglutide for 2 weeks. No phase 1 studies involved dosing beyond 2 weekly doses.

Single Dose Pharmacokinetics in Healthy Subjects:

In healthy subjects five cohorts received either placebo injections or two weekly, escalating sc doses of albiglutide on Day 1 and Day 8. Summary of pharmacokinetics parameters following Day 1 dosing on Week 1 in healthy subjects is shown in Table 6.

Table 6: Summary of PK Parameters in Healthy Subjects Following Single SC Dose of Albiglutide.

Parameter	Dose[1]			
	Cohort 2 3 mg n=6	Cohort 3 16 mg n=6	Cohort 4 48 mg n=6	Cohort 5 80 mg n=5
Week 1 PK Parameters				
AUC(0-7days)[2], μg.hr/mL	18.8 (31.6)	133 (29.2)	519 (50.2)	1170 (33.5)
Cmax[2], μg /mL	0.137 (37.4)	0.967 (26.6)	3.95 (52.3)	8.92 (29.2)
Tmax[3], days	4.0 (3.0-5.0)	3.4 (1.5-5.0)	4.3 (3.0-7.0)	3.4 (3.0-5.0)
Week 1, Day 2 PK Parameters				
AUC(0-24)[2], μg.hr/mL	2.38 (26.8)	18.4 (41.3)	65.5 (71.3)	156 (50.3)
AUC(0:30-4:30)[2], μg.hr/mL – Breakfast	0.323 (32.1)	2.56 (52.6)	9.35 (57.4)	20.2 (60.1)
AUC(4:30-8:30)[2], μg.hr/mL – Lunch	0.362 (27.7)	2.85 (45.9)	10.1 (67.5)	23.3 (55.1)
AUC(10:30-14:30)[2], μg.hr/mL – Dinner	0.414 (23.9)	3.23 (39.4)	11.1 (80.0)	27.5 (50.1)

Source Data: Table 12.3

1. Cohort 1 (0.25 mg) concentrations were below quantifiable levels (BQL)
2. Geometric mean (%CV)
3. Median (minimum, maximum)

Source: Sponsor's report on Summary of Clinical Pharmacology Pg: 14

Statistical Analysis for dose proportionality based on AUC (0-7 days) and C_{max} for the 3, 16, 48 and 80 mg albiglutide following single dose administration on week 1 is shown in Table 7. For both parameters, the estimated mean slope was greater than one and the corresponding 90% CIs did not contain unity, indicating a greater than proportional increase in albiglutide exposure with increasing dose following single dose administration of albiglutide. In healthy subjects albiglutide had a relatively slow rate of absorption and elimination with t_{max} occurring 3 to 4 days post-dose and mean terminal elimination half-life ranging from 6 to 8 days.

Table 7: Statistical Analysis for Dose Proportionality following Single Dose Administration of 3, 16, 48 and 80 mg Dose of Albiglutide.

Parameter	Estimated Mean Slope	Standard Error	Degrees of Freedom	90% CI
AUC	1.24	0.058	21	(1.14, 1.34)
Cmax	1.25	0.060	21	(1.15, 1.35)

Source Data: Table 12.4

Source: Sponsor's report on Summary of Clinical Pharmacology Pg: 14

Single Dose Pharmacokinetics in T2DM Subjects:

Similar to healthy subjects, in T2DM subjects three cohorts were randomized to receive two weekly sc injections of albiglutide or placebo on Days 1 and 8. In T2DM subjects, the rate of absorption was slow with t_{max} occurring 3 to 5 days post dose and mean terminal elimination half-life of albiglutide ranging from 5.7 to 6.8 days. T_{max} and $t_{1/2}$ were similar across all dose levels. Summary of pharmacokinetics parameters following dosing on Day 1 of week 1 and Day 8 of week 2 in T2DM subjects is shown in Table 8 .

Table 8: Summary of PK Parameters in T2DM Subjects Following Two Weekly SC Dose of Albiglutide.

Parameter	Doses of Albiglutide					
	9 mg (N=14)		16 mg (N=12)		32 mg (N=13)	
	Week 1	Week 2	Week 1	Week 2[4]	Week 1	Week 2
AUC(0-24 hr)[1] (µg*hr/mL)	6.60 (93.1)	22.8 (43.9)	10.3[3] (92.2)	18.94 (54.2)	12.7 (99.4)	28.8 (57.9)
AUC(0-7 days)[1] (µg*hr/mL)	89.4 (45.1)	151 (43.1)	73.6 (90.4)	147 (40.0)	101 (77.5)	214 (55.2)
Cmax[1] (ng/mL)	828 (51.4)	1062 (43.4)	833 (59.7)	1170 (29.3)	877 (76.2)	1540 (52.7)
Tmax[2] (days)	5.00 (0.78-7.00)	2.99 (0.15-5.00)	3.00 (1.50-7.00)	5.00 (1.50-7.00)	5.00 (3.00-7.00)	3.00 (0.35–5.00)
tlag[2] (hr)	3.50 (0.00-18.5)	--	0.00 (0.00 - 8.50)	--	0.00 (0.00-8.50)	--
t1/2[1] (days)	--	6.80 (40.7)	--	6.43 (21.0)	--	5.73 (28.9)

Source Data: Study GLP106073 Table 17.

1. Geometric mean (%CV).
2. Median (range).
3. N = 11.
4. N = 10.

Source: Sponsor's report on Summary of Clinical Pharmacology Pg:17

Plasma albiglutide AUC (0-7 days) and C_{max} following administration in Week 1 increased in a less-than-dose-proportional manner in this study. The slope estimate (90% CI) was 0.28 (0.05, 0.51) for AUC (0-7 days) and 0.30 (0.08, 0.51) for C_{max}. Following two weekly sc dose of albiglutide, the accumulation ratio ranged from 1.7 to 2.1 fold at all dose levels.

Over the evaluated dose range of 9 mg to 32 mg, the PK of albiglutide showed an unexplained less than dose-proportional increase with dose. This is inconsistent with healthy volunteers where a more than dose-proportional increase in exposure was observed with increase in dose.

Reviewers Comment:

1) ***During drug development albiglutide drug substance is manufactured using Process 1, Process 2 and Process 3. Also, there are certain differences in the formulation of the final products using different drug substances. Process 1 drug substance and formulation is used in some Phase 1 studies, Process 2 drug substance and formulation is used in most of the Phase 2 and Phase 3 studies. Process 3 drug substance and formulation is the proposed to-be-marketed formulation. Sponsor conducted a clinical bridging study between drug substance and formulation from Process 2 and Process 3.***

2) ***Early Phase 1 pharmacokinetics studies as outlined above used the drug substance from Process 1 and the formulation used was not similar to the proposed to-be-marketed formulation. Thus, the study results from these Phase 1 studies are exploratory in nature and should not be translated into the product label.***

3) ***Sponsor did not conducted any clinical study to bridge the differences between the formulations and drug substance used in this early Phase 1 PK study to the proposed to-be marketed formulation. However, sponsor conducted nonclinical PK/PD studies to demonstrate that there is no difference on the pharmacokinetics and pharmacodynamics between drug substance and formulation from process 1 and process 2. Please refer to non clinical review by Dr. Wange for further details***

4) ***Sponsor gave no rationale for the differences seen in the exposure of albiglutide in T2DM subjects and healthy subjects.***

Multiple Dose Pharmacokinetics in T2DM subjects

Multiple dose trough concentrations in T2DM subjects were assessed in pivotal bioequivalence study (study# 114856). Trough concentrations following 30 mg sc multiple doses of albiglutide are presented in Table 9. Week 5 represents the first dosing and week 17 is the last dosing period. At steady state the trough concentration following 30 mg weekly dose is around 2500 ng/mL

Table 9: Summary of Albiglutide Plasma Concentrations by Nominal Sampling Time and Treatment Arm

Nominal Sampling Time	Process 2		Process 3	
	n	Mean (SD)	n	Mean (SD)
Week 5 Trough	131	10.6 (34.8)	135	8.70 (25.5)
Week 9 Trough	127	2421 (1064)	130	2520 (912)
Week 13 Trough	126	2353 (984)	127	2356 (987)
Week 17 Trough	123	2360 (1006)	125	2437 (1089)
Week 25 Follow-Up	121	28.2 (291)	123	14.4 (160)

Source Data: Table 14.4-1.1

Reviewers Comment: The Process 3 drug substance and the formulation used in this study is the proposed to be marketed drug substance and formulation. Thus, the results of this study can be used for the purpose of drug labeling.

2.4.2 What are the characteristics of drug absorption?

The absolute bioavailability of albiglutide following sc administration has not been evaluated. Based on data from pivotal BE study, following sc administration of a single 30 mg dose to patients with type 2 diabetes, the absorption half-life of albiglutide is approximately 1.5 days and maximum concentrations were reached 3 to 5 days post dose. Following 30 mg sc dose, the mean peak albiglutide concentration (C_{max}) was 1.74 µg/mL and mean area under the time concentration curve (AUC) was 465 µg•hr/mL (Please refer to 2.7.1 for further details). Similar exposure is achieved with sc administration of albiglutide in the abdomen, thigh, or upper arm (Please refer to section 2.6.7 for further details).

2.4.3 What are the characteristics of drug distribution?

As albiglutide is an albumin fusion molecule, plasma protein binding has not been evaluated. Based on full PK sampling from a bioequivalence study (Study GLP114856) after a single dose of albiglutide, the mean estimate of apparent volume of distribution (V/F) is approximately 11 L (Please refer to section 2.7.1 for further details).

2.4.4 What are the characteristics of drug metabolism and elimination?

Albiglutide is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Classical biotransformation studies have not been performed. Based on full PK sampling from a bioequivalence study (Study GLP114856) after a single dose of albiglutide, the mean

estimate of apparent clearance (CL/F) is 64.5 mL/hr (Please refer to section 2.7.1 for further details).

2.4.5 What are the pharmacodynamic properties of albiglutide following single and multiple dose in healthy adults?

In healthy subjects five cohorts received either placebo injections or two weekly, escalating sc doses of albiglutide on Day 1 and Day 8. Doses of 0.25, 3, 16, 48 and 80 mg of albiglutide was administered on Week 1 (Day 1) and on Week 2 (Day 8), doses of 1, 6, 24, 60 and 104 mg albiglutide was administered. Following two weekly doses of albiglutide the pharmacodynamic profile of albiglutide in healthy subjects showed dose-dependent trend in reductions of glucose weighted mean AUC levels, see Table 10. No consistent dose-dependent changes were seen in glucagon or insulin levels or in insulin/glucose ratios or insulin/glucagon ratios.

Table 10: Summary of Glucose Weighted Mean AUC Comparisons by Dose vs Placebo (mg/dL)

Parameter	Cohort 1 0.25 mg+1mg LS Means Difference (90% CI)	Cohort 2 3 mg+6 mg LS Means Difference (90% CI)	Cohort 3 16 mg+24 mg LS Means Difference (90% CI)	Cohort 4 48 mg + 60 mg LS Means Difference (90% CI)	Cohort 5 80 mg+104 mg LS Means Difference (90% CI)
AUC (0-24 – Daily)					
Day 2	2.19 (-1.19, 5.58)	-0.21 (-3.62, 3.20)	-4.23 (-7.66, -0.79)	-8.80 (-12.3, -5.34)	-11.0 (-14.6, -7.35)
Day 9	2.74 (-1.53, 7.01)	2.23 (-2.06, 6.53)	-0.60 (-4.93, 3.74)	-2.26 (-6.62, 2.11)	-10.0 (-14.6, -5.42)
AUC (0:30-4:30 – Breakfast)					
Day 2	-0.38 (-6.84, 6.09)	-0.36 (-6.87, 6.16)	-1.14 (-7.91, 5.64)	-6.94 (-13.2, -0.67)	-10.8 (-17.6, -3.96)
Day 9	0.24 (-5.99, 6.48)	-0.65 (-6.93, 5.63)	-2.51 (-9.04, 4.02)	-1.56 (-7.60, 4.49)	-11.9 (-18.4, -5.29)
AUC (4:30-8:30 – Lunch)					
Day 2	2.51 (-2.77, 7.80)	1.01 (-4.45, 6.48)	-8.09 (-13.5, -2.66)	-7.56 (-12.9, -2.25)	-12.2 (-17.9, -6.55)
Day 9	9.33 (3.69, 15.0)	0.91 (-4.92, 6.75)	1.15 (-4.64, 6.95)	-1.35 (-7.01, 4.31)	-8.32 (-14.3, -2.29)
AUC (10:30-14:30 – Dinner)					
Day 2	4.75 (-1.90, 11.4)	-0.99 (-7.74, 5.76)	3.03 (-3.68, 9.75)	-11.4 (-18.1, -4.76)	-15.8 (-22.9, -8.77)
Day 9	-1.44 (-9.76, 6.88)	9.18 (0.72, 17.6)	3.15 (-5.25, 11.5)	-4.69 (-13.0, 3.63)	-16.9 (-25.7, -8.08)

Source Data: Table 13.10

Source: Sponsor's report on Summary of Clinical Pharmacology

2.4.6 What are the pharmacodynamic properties of albiglutide in T2DM subjects?

Several studies evaluate the pharmacodynamics of albiglutide in T2DM subjects. Repeat dose escalation study (Study # GLP106073), where subjects receive two weekly doses of 9 mg, 16 mg and 32 mg albiglutide and standardized meal (which contained 50% carbohydrate, 30% fat, and 20% protein) evaluated PD. PD analysis was conducted on Day 2 and Day 9 (which is approximately 24 hr after injection) at the timepoint of anticipated maximum concentrations of albiglutide at each dose level. The PD profile of

albiglutide in subjects with T2DM showed dose-dependent reductions in glucose weighted mean AUC (0-24 hr) and fasting glucose as shown in Table 11.

Table 11: Summary of Fasting Glucose and Glucose Weighted Mean AUC Comparisons by Dose vs. Placebo (mg/dl) (Study GLP106073)

Parameter	Doses of Albiglutide		
	9 mg	16 mg	32 mg
	LS Means Difference (95% CI)	LS Means Difference (95% CI)	LS Means Difference (95% CI)
Fasting			
Day 2	-7.36 (-25.9, 11.2)	-22.9 (-40.7, -4.99)	-26.7 (-46.3, -7.06)
Day 9	-23.8 (-47.9, -0.28)	-32.5 (-57.3, -7.74)	-50.7 (-75.4, -26.0)
AUC(0-24 hr – Daily)			
Day 2	-25.2 (-43.0, -7.43)	-28.0 (-45.7, -10.3)	-34.8 (-54.1, -15.5)
Day 9	-31.0 (-55.6, -6.36)	-34.8 (-60.6, -8.88)	-56.4 (-82.2, -30.5)
AUC(0:30-4:30 hr – Breakfast)			
Day 2	-13.0 (-34.2, 8.14)	-41.6 (-62.2, -21.0)	-47.4 (-68.8, -26.0)
Day 9	-18.0 (-49.9, 13.9)	-46.5 (-79.3, -13.7)	-65.5 (-98.4, -32.6)
AUC(4:30-8:30 hr – Lunch)			
Day 2	-37.4 (-60.9, -13.9)	-35.6 (-59.5, -11.6)	-42.9 (-67.7, -18.2)
Day 9	-42.0 (-70.6, -13.4)	-38.8 (-69.1, -8.44)	-57.3 (-87.6, -27.0)
AUC(10:30-14:30 hr – Dinner)			
Day 2	-33.3 (-54.7, -12.0)	-34.5 (-57.1, -11.83)	-34.2 (-56.9, -11.5)
Day 9	-41.1 (-67.3, -14.9)	-33.8 (-63.3, -4.24)	-54.0 (-82.1, -25.9)

Source Data: Study GLP106073 Table 21.

1. For prior to Day 8 dosing assessments, all subjects are included except two subjects who were misdosed. For after Day 8 dosing assessments, three subjects were misdosed and are excluded.

Source: Sponsor's report on Summary of Clinical Pharmacology Pg:17

Reviewers Comment:

1) ***Early Phase 1 pharmacodynamics studies as outlined above used the drug substance from Process 1 and formulation which was not similar to the proposed to-be-marketed formulation. Thus, the study results from these Phase 1 studies are exploratory in nature and should not be translated into the product label. As stated under reviewers' comments above, Process 1 and Process 2 substances are only bridged using nonclinical PK/PD study.***

2.4.7 What are the pharmacodynamic effects of albiglutide on counter regulatory hormone response and recovery from hypoglycemia in T2DM subjects?

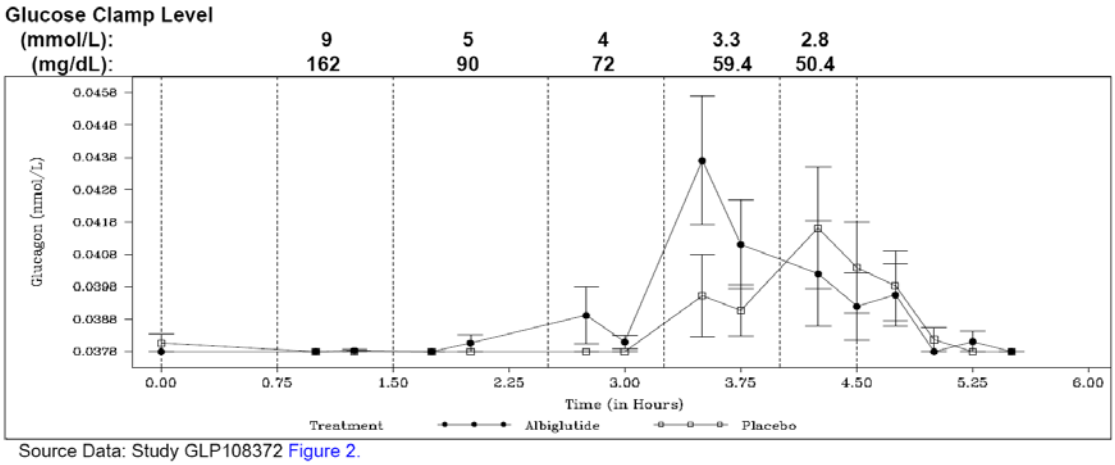
Sponsor conducted a stepped glucose clamp study designed to investigate the effect of albiglutide on counter-regulatory hormone responses and recovery from hypoglycemia in subjects with T2DM who were on a current regimen of diet and exercise or oral antidiabetic drugs (e.g., sulfonylurea, meglitinides, or dipeptidyl peptidase-4 inhibitors)(Study#108372).

In this trial a single dose of albiglutide (50 mg) or placebo was given 3 days before the start of the stepped hyper- and hypoglycemic clamp with glucose plateaus of 9.0, 5.0, 4.0, 3.3, and 2.8 mmol/L (162, 90, 72, 59, and 50.4 mg/dL, respectively). In this study each

glucose target level was maintained for 30 minutes before continuing to the next glucose target level.

A total of 44 subjects were randomized (22 to albiglutide and 22 to placebo). The majority of subjects in each treatment group (86%) were on background metformin therapy on Day 1. Males (n=10) and females (n=12) were evenly distributed in subjects randomized to albiglutide and placebo. The primary objective of the study was to assess the effect of albiglutide on glucagon secretion during hypoglycaemia. Secondary objectives included the assessment of other counter regulatory responses during hypoglycaemia and albiglutide's impact on insulin secretion.

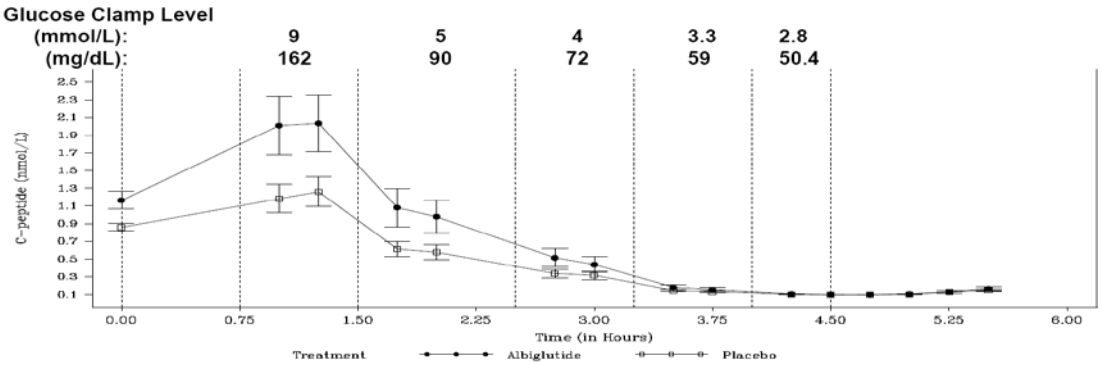
Figure 12 shows glucagon response at each clamped glucose concentration (9, 5, 4, 3.3 and 2.8 mmol/L). Baseline values for fasting glucagon on Day 4 were similar among the albiglutide and placebo treatment groups. When glucose was clamped at a hypoglycemic level (3.3 mmol/L; 59.4 mg/dL) the mean glucagon level rose in both groups, those in the albiglutide 50 mg group had statistically significant increase was observed as compared to the placebo group. The glucagon levels at the hypoglycemic plateau of 2.8 mmol/L (50.4 mg/dL) were not different between the treatment groups and both groups recovered to baseline levels an hour after the insulin infusion was stopped.



Source Data: Study GLP108372 Figure 2.
Note: Values below the lower limit of quantification (0.0378 nmol/L) were set to the quantification limit for analysis.

Figure 12: Glucagon Over Time at Each Glucose Clamp Level (Pharmacodynamic Population)

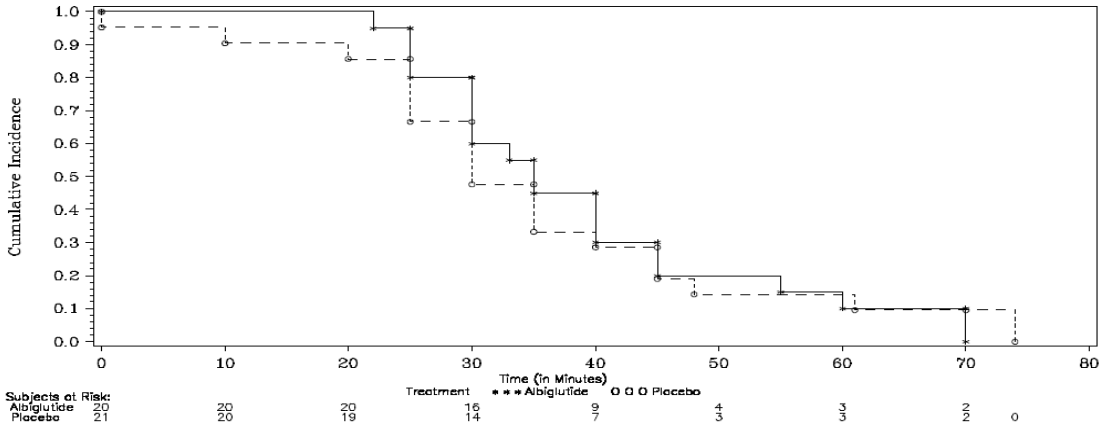
Figure 13 show C-peptide response during the 5 glucose target periods. Baseline values for fasting C peptide on Day 4 were similar between the albiglutide and placebo treatment groups. C peptide levels showed a statistically significant increase during the hyperglycemic plateau of the glucose clamp procedure. The C-peptide levels in the albiglutide group were significantly higher than those in the placebo treatment group at the glucose levels of 9 nmol/L and at 5 nmol/L. Starting at the euglycemic plateau (4 mmol/L [72 mg/dL]), the differences between the treatment groups were not different indicating glucose dependent insulin secretion properties of albiglutide.



Source Data: Study GLP108372 Figure 3.
Note: Values below the lower limit of quantification (<0.10 nmol/L) were set to the quantification limit for analysis.

Figure 13: C-peptide (nmol/L) Over Time at Each Glucose Clamp Level (Pharmacodynamic Population)

In this study sponsor also assessed the effect of albiglutide on recovery time of plasma glucose levels to at least 3.9 mmol/L (70 mg/dL) from the hypoglycemic clamp level of 2.8 nmol/L (50.4 mg/dL). Figure 14 shows a Kaplan-Meier plot of the time to recovery for the 2 treatment groups. The median time to recovery was 35.00 minutes (95% CI = 30.00, 45.00) for the albiglutide 50 mg group and 30.00 minutes (95% CI = 25.00, 40.00) for the placebo group. There was no significant difference in the recovery time between albiglutide and placebo.



Source Data: Figure 14.2.10.
Note: Time to recovery from hypoglycemia to 3.9 mmol/L (70 mg/dL) was calculated as the time in minutes between switching off of the insulin infusion and reaching the level of 3.9 mmol/L (70 mg/dL). Cumulative incidence is defined as the probability that hypoglycemia recovery did not occur at the specified time. The last 2 subjects in albiglutide group recovered to 3.9 mmol/L level at 70 minutes.

Figure 14: Kaplan-Meier Plot of Time to Recover From Hypoglycemia to 3.9 mmol/L (70 mg/dL) (Pharmacodynamic Population)

In conclusion, a single dose of albiglutide (50 mg) stimulated the glucose dependent release of c-peptide also demonstrated that it did not impair other counter-regulatory hormone response to hypoglycemia as determined by levels of glucagon, epinephrine, norepinephrine, cortisol, and growth hormone.

2.5 Intrinsic Factors

2.5.1 What intrinsic factors (e.g., age, gender, race, weight, height, , pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response(PD)?

Renal Impairment:

Sponsor conducted an adaptive, non-randomized, open-label, single-dose study to assess the PK and safety of albiglutide in subjects with T2DM with varying degrees of renal function. This study was conducted in two stages. In Stage 1, all subjects in Cohort 1 (normal renal function, n=7) and Cohort 2 (moderate/severe renal function, n=7) received a single sc dose of 30 mg albiglutide.

As shown in Table 12, following dosing in stage 1, the exposures was comparable in subjects with normal and impaired renal function.

Table 12: Pharmacokinetic Parameters of Albiglutide in Normal and Renally Impaired Patients (Stage 1)

Parameter (unit)	Renal Function[1]	N	Geometric LS Means (%CV)	Ratio of Geometric LS Means (Impaired vs Normal)[1]	90% CI of Ratio (Impaired vs Normal)[1]
AUC(0–∞) (µg.hr/mL)	Normal	5	326 (29.9)	–	–
	Impaired	5	331 (40.9)	1.013	(0.674, 1.524)
AUC(0–312) (µg.hr/mL)	Normal	7	209 (31.9)	–	–
	Impaired	7	195 (36.6)	0.929	(0.676, 1.277)
Cmax (ng/mL)	Normal	7	937.4 (30.2)	–	–
	Impaired	7	818.3 (38.0)	0.873	(0.636, 1.199)

Source: Study GLP108370 Table 22 and Table 14.2-2.1.
CI = confidence interval, LS = least squares
Note: An analysis of variance was performed on natural logarithms of PK parameters. The model included cohort as fixed term effect.
1. Cohort 1: Normal renal function (estimated glomerular filtration rate >80 mL/min); Cohort 2: Impaired renal function = Moderate-to-severe renal impairment (estimated glomerular filtration rate ≥20 mL/min, <50 mL/min).

Based on comparable exposures in subjects with normal renal function and those with moderate to severe renal function observed in Stage 1, subjects with mild renal impairment were not enrolled in Stage 2. Stage 2 of the study enrolled additional subjects with normal renal function (n=3), moderate renal impairment (n=7) and severe renal impairment (n=7). In addition, subjects requiring hemodialysis were also enrolled (n=10).

In contrast to results from stage 1, exposures were higher in renally impaired patients as compared to normal renal function subjects (Table 13). Sponsor's further investigation concluded that this increase in exposure in renally impaired patient during stage 2 is related to bioanalytical issues. Sponsor reported that there is a change in assay methodology during this time period which resulted in upward shift of exposures in renally impaired patients which were analysed by the new method, as contrast to normal renal function subjects in stage 2 which were analysed by similar method as in stage 1. Thus, the exposure in normal renal function subjects were similar in stage1 and stage 2 of dosing, whereas due to change in analytical methodology the exposure were different in renally impaired patients during stage 1 and stage 2 of dosing. Please refer to section 2.8 for further details on bioanalytical method as assay shift related issue.

In this study, sponsor after accounting for assay shift based on reanalysis of very limited samples concluded that there is an approximately 30-40% increase in exposure in renally impaired patients when compared to healthy subjects.

Table 13: Pharmacokinetic Parameters of Albiglutide in Renally Impaired Patients (Stage 2 of Study GLP108370)

Parameter (unit)	Renal Function[1]	N	Geometric LS Means (%CV)
AUC(0–∞) (µg.hr/mL)	Normal[2]	3	256 (16.9)
	Moderate	5	546 (16.6)
	Severe	7	723 (73.6)
	Hemodialysis	10	445 (38.2)
AUC(0–312) (µg.hr/mL)	Normal[2]	3	167 (45.8)
	Moderate	7	405 (19.1)
	Severe	7	438 (73.4)
	Hemodialysis	10	307 (30.9)
Cmax (ng/mL)	Normal[2]	3	780 (42.9)
	Moderate	7	1738 (20.3)
	Severe	7	2032 (76.5)
	Hemodialysis	10	1525 (44.4)

Source: Study GLP108370 Table 23, Table 24, Table 14.2-2.2.
CI = confidence interval, LS = least squares
1. Normal renal function (estimated glomerular filtration rate >80 mL/min); Moderate renal impairment (estimated glomerular filtration rate ≥30 mL/min, <50 mL/min); Severe renal impairment (estimated glomerular filtration rate <30 mL/min) not requiring hemodialysis.
2. Normal subjects were analyzed around July 2010 at the time of the ELISA shift.

Reviewer's Comment: Due to the bioanalytical issues this study result are just exploratory in nature and no definitive conclusions can be drawn from it. Sponsor reports that there is an upward shift in assay concentrations during stage 2 of the dosing which might impact the exposures level in renally impaired subjects. Sponsor did not fully reanalyze all the study samples, but based on few reanalysis of few samples they concluded that patients with moderate to severe renal impairment have

increase in exposure of 30-40%. Sponsor is not recommending any dose adjustment in renally impaired patients which can be supported by a dedicated phase 3 study in patients with mild, moderate and severe renally impaired patients. Population PK analysis of Phase1-3 data provides information on exposure changes in renally impaired patients.

Hepatic Impairment:

No formal studies of albiglutide have been performed in patients with hepatic impairment. Therapeutic proteins such as albiglutide are catabolised by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of albiglutide.

Age, Gender, Race and Body Weight: Based on the population pharmacokinetic analysis with data collected from 1113 subjects, age, gender, race, and body weight had no clinically relevant effect on the pharmacokinetics of albiglutide. Please refer to Pharmacometrics review Appendix 4.3 for further details.

2.6 Extrinsic Factors

2.6.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Given the structure and large molecular size of albiglutide (~73 kDa) and expected proteolytic degradation, it is not expected that this molecule would pass the cell membrane and gain access to the drug metabolizing enzymes and hence it is not expected that other drugs will influence the pharmacokinetics of albiglutide.

2.6.2 Is the drug a substrate, inhibitor or an inducer of CYP enzymes?

Albiglutide is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. No specific preclinical studies were undertaken to examine drug interactions. However, the potential for albiglutide to induce hepatic CYP enzymes was determined following repeated sc administration of albiglutide to monkeys as part of a 5 week toxicity study.

Twice weekly sc administration of 5, 15, or 50 mg/kg/week albiglutide for 5 weeks resulted in minimal increases in CYP1A2 mRNA levels in male monkeys and a minimal increase in CYP2B17 mRNA levels in female monkeys, although the increases were not dose-dependent. Treatment of male monkeys with albiglutide showed slight to notable increases (up to 2.1-fold) at all dose levels in the activities CYP1A. In female monkeys, no change in CYP1A activity was observed at any dose level. In this same study, there was little or no effect of albiglutide treatment on hepatic microsomal protein, total CYP content, or the activity of CYP2B, CYP2E, CYP3A, and CYP4A.

Table 14: Effect of GSK716155A on CYP mRNA in Male Cynomolgus Monkey Liver

Male Monkeys:

Cytochrome P450	mRNA Fold Change Over Control											
	Control			5 mg/kg/week			15 mg/kg/week [1]			50 mg/kg/week		
	Mean	±	SD	Mean	±	SD	Mean			Mean	±	SD
CYP1A1	1.0	±	0.5	1.4	±	0.5	0.97			1.8	±	1.6
CYP1A2	1.0	±	0.9	5.2	±	4.2	5.1			5.2	±	3.5
CYP2B17	1.0	±	0.9	1.2	±	0.7	1.1			1.5	±	0.6
CYP2C	1.0	±	0.1	1.3	±	0.2	1.3			1.0	±	0.4
CYP2D17	1.0	±	0.4	1.7	±	0.8	1.2			0.9	±	0.7
CYP2E1	1.0	±	0.6	1.3	±	0.6	0.79			1.2	±	0.8
CYP3A8	1.0	±	0.9	0.49	±	0.3	0.52			0.49	±	0.4

Values are expressed as a Mean ± Standard Deviation of 3 animals except for the 15 mg/kg/week group which was 2 animals.
1. The 15 mg/kg/week group had 2 animals because the tissue was not collected for the other animal.

Female Monkeys:

Cytochrome P450	mRNA Fold Change Over Control											
	Control			5 mg/kg/week			15 mg/kg/week			50 mg/kg/week		
	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD
CYP1A1	1.0	±	0.4	1.7	±	1.4	1.1	±	0.5	1.2	±	0.7
CYP1A2	1.0	±	0.2	2.1	±	0.8	0.85	±	0.7	1.5	±	1.7
CYP2B17	1.0	±	0.2	3.0	±	1.2	1.9	±	1.4	2.4	±	0.2
CYP2C	1.0	±	0.4	1.8	±	0.2	1.1	±	0.7	1.1	±	0.0
CYP2D17	1.0	±	0.5	2.1	±	0.9	2.5	±	1.2	1.8	±	1.2
CYP2E1	1.0	±	0.6	1.4	±	0.1	1.1	±	0.2	0.68	±	0.3
CYP3A8	1.0	±	0.8	0.33	±	0.2	1.2	±	0.5	0.30	±	0.2

Values are expressed as a Mean ± Standard Deviation of 3 animals.

Reviewers Comment: An increase in CYP1A mRNA and enzyme activity was seen in male monkeys following multiple dose administration of albiglutide. Although a five fold increase in mRNA levels for CYP1A was observed only 2 fold increase in activity was seen in male monkeys only. No increase in CYP1A activity was seen in female monkeys. In addition in a clinical drug-drug interaction albiglutide following multiple dose showed no changes in the exposure of s-warfarin (which is metabolized by CYP1A). Thus, these preclinical findings of increase in CYP1A activity only in male species are of minimal clinical relevance.

2.6.3 Is there a known mechanistic basis for pharmacokinetics/ pharmacodynamic drug-drug interactions, if any?

Albiglutide, like other GLP-1 receptor agonists, slows gastric emptying time and thus it can potentially alter the rate of absorption of orally administered drugs. The effect of albiglutide in delaying gastric emptying time is discussed in section 2.6.4. Also, the impact of gastric emptying effect of albiglutide on the commonly prescribed medications for patients with T2DM, namely digoxin, warfarin, simvastatin, and oral contraceptives is further discussed in section 2.6.5.

2.6.4 What is the effect of albiglutide on gastric emptying time?

Glucagon-like peptide-1 and GLP-1 mimetics are known to cause delays in gastric emptying. Altered gastric motility may also affect the pharmacokinetics and possibly the efficacy of concomitant medications. To study the effect on albiglutide on gastric emptying time sponsor conducted a gamma scintigraphy study (Study#GLP107030).

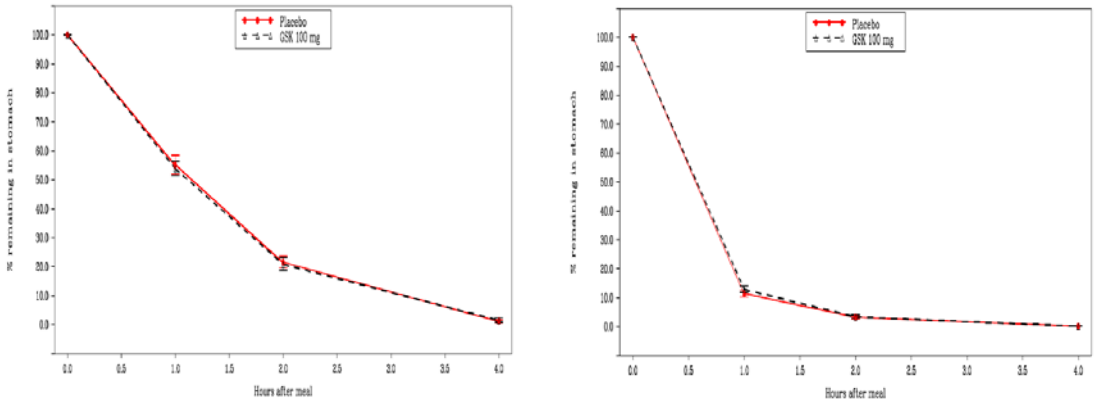
The study was a single-center, single-blind, randomized, placebo-controlled study to determine the effect of single dose sc 100 mg of albiglutide dose on gastric emptying in healthy subjects. In this study all subjects received placebo on Day 1 and scintigraphy assessments on Day 4. On Day 8, subjects were randomly assigned to receive albiglutide or placebo followed by scintigraphy assessments on Day 11. In this study sponsor used a single dose of 100 mg to approximate a clinically relevant albiglutide steady-state concentration.

To examine gastric emptying, this study monitored a conventional dual-isotope gastric emptying meal, consisting of scrambled eggs radiolabeled with 150 μCi of 99m-technetium sulfur colloid (^{99m}Tc-sulfur colloid) between 2 pieces of toasted white bread and water containing 50 μCi of 111indium-diethylenetriaminepentaacetic acid (^{111}In-DTPA). For analysis of gastric emptying, images were analyzed to determine gastric counts based on ^{99m}Tc-sulfur and ^{111}In-DTPA. The percent radioactivity of ^{99m}Tc-sulfur and ^{111}In-DTPA that was retained in the stomach at prescribed time points was used as the primary index of gastric emptying of solids and liquids, respectively.

Figure 15 and Table 15 presents a summary of the gastric emptying time at day 4 (placebo) and at day 11 (72 hours after albiglutide dosing) for both solid and liquid meals. Following albiglutide administration, there was a statistically significant increase in the gastric emptying t½ for the albiglutide group for both solids and liquids. For solids, the gastric emptying t½ increased from 1.14 hours at Day 4 to 2.23 hours at Day 11 (p=0.0112). For liquids, gastric emptying t½ increased from 0.28 hours at Day 4 to 0.69 hours at Day 11 (p=0.0018).

Day 4

Solid Meal **Liquid Meal**



Day 11

Solid Meal **Liquid Meal**

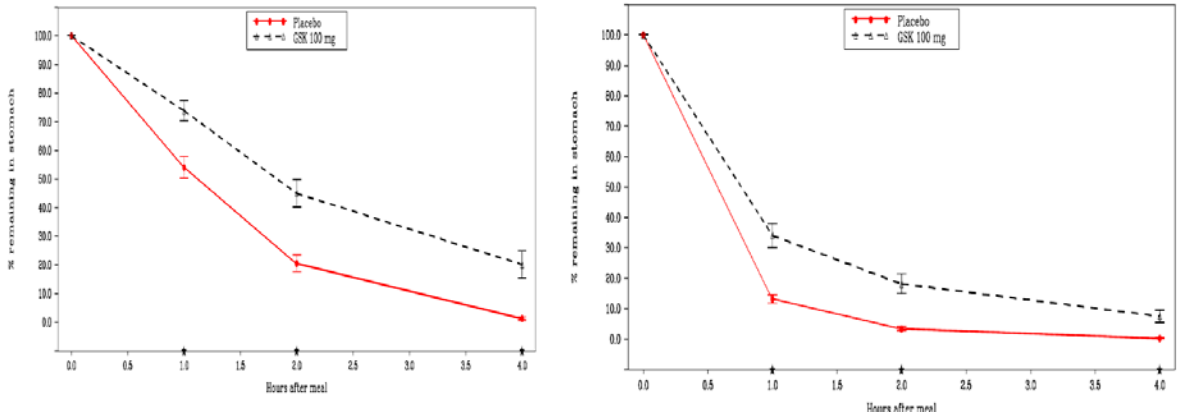


Figure 15: Mean (SE) Approximate Percent of Solid and Liquid Meal Remaining in the Stomach Day 4 (Placebo) vs on Day 11 (Albiglutide 100 mg Dose).

Table 15: Summary of Time (hours) to 50 Percent Gastric Emptying following Placebo Dosing at Day 4 and Albiglutide Dosing on Day 11

	Placebo (N=17)	albiglutide 100 mg (N=17)	p-value[a]
Gastric emptying of solids			
Day 4 (Baseline)			
Mean (SD)	1.15 (0.26)	1.14 (0.24)	
Day 11 (after albiglutide or placebo administration)			
Mean (SD)	1.15 (0.36)	2.23 (1.66)	
p-value[b]	0.9593	0.0112	0.0072
Gastric emptying of liquids			
Day 4 (Baseline)			
Mean (SD)	0.25 (0.12)	0.28 (0.07)	
Day 11 (after albiglutide or placebo administration)			
Mean (SD)	0.27 (0.13)	0.69 (0.46)	
p-value[b]	0.6988	0.0018	0.0015

Data Source: Table 14.2 -1.1 and Table 14.2 -1.2
PD = pharmacodynamic.
a. Albiglutide compared with placebo at Day 11; based on analysis of covariance model (change = treatment + Baseline), where change is the response variable (Day 11 – Day 4).
b. Compared with Baseline.

Source: Sponsor's Study report for Study GLP107030

Reviewers Comment:

1) ***Albiglutide has been found to delay gastric emptying as compared to placebo (albiglutide approximately doubled the time taken to achieve 50% gastric emptying).***

2) ***The results of this study should be interpreted with caution because the drug substance (Process 1) and formulation used in this study is not the final proposed to be marketed formulation. In addition, there is a lack of clinical bridge between***

the drug substance and formulation used in this study to the proposed to-be-marketed formulation.

3) ***Although a delay is gastric emptying effect was observed in this study, clinical drug-drug interaction study following multiple dose of albiglutide showed no clinically meaningful difference in drug exposures of warfarin, digoxin, simvastatin and oral contraceptives.***

2.6.5 What is the effect of albiglutide co-administration on the pharmacokinetics of other drugs?

Albiglutide has been found to delay gastric emptying as compared to placebo (albiglutide approximately doubled the time taken to achieve 50% gastric emptying), as do other GLP-1R agonist, and thus has the theoretical potential to alter the rate of absorption of orally administered drugs. The drug-drug interaction (DDI) program for albiglutide assessed the effect of albiglutide on a number of commonly prescribed medications for patients with T2DM, namely digoxin, warfarin, simvastatin, and oral contraceptives.

The study designs for all the DDI studies were similar in this application, where the effect of albiglutide on the pharmacokinetic of other drugs was assessed at approximate albiglutide steady state exposures. In all the DDI studies, a dose of 50 mg weekly was employed which is the maximal dose administered during the Phase III development program.

As shown in Table 16, 50 mg once weekly dose of albiglutide at steady state has no clinically meaningful effect on the pharmacokinetics of digoxin, warfarin, and simvastatin (following single dose administration of these drugs). Also, albiglutide at steady state does not alter the pharmacokinetics of oral contraceptive given as multiple doses.

Reviewers Comment: This reviewer agrees with the sponsor's proposed recommendations of no dose adjustment for co-administration with warfarin, oral contraceptives, digoxin and simvastatin. In the case of simvastatin, there was an approximately two fold increase in Cmax and 40% increase in AUC (exposure) of simvastatin acid. The current knowledge on the relationship of Cmax or AUC of simvastatin acid to the rhabdomyolysis or myopathy related adverse events is not clear. In addition, based on sponsor's report of integrated analysis of safety the incidence rate of rhabdomyolysis or myopathy related adverse events were similar in patients on simvastatin taking albiglutide or other comparator. Thus, based on the limited information on relationship of exposure changes of simvastatin acid on the safety, we agree with the sponsor's recommendation of no dose adjustment of simvastatin when given with albiglutide. However, due to the increased exposures and Cmax for simvastatin acid we recommend that caution should be exercised for patient who are on simvastatin dose of 20 mg or higher and starts albiglutide.

Table 16: Effect of Albiglutide on the Pharmacokinetics of Co-administered Drugs

Albiglutide (Dose Regimen)	Co-administered Drug (Dose Regimen)	Major Clearance Pathways of Co-administered Drug	Effect on Co-administered Drug Exposure GMR (90% CI)	
			AUC_{inf}	C_{max}
Albiglutide (4 Doses of 50 mg Given Once Weekly on 2nd dosing Period)	Oral Contraceptive Brevicon Norethindrone (2 Dosing Periods of 21 days, 0.5 mg)	Metabolism by CYP3A4	1.09 (1.06, 1.14)	**1.20 (1.11, 1.29)**
	Ethinyl Estradiol (2 Dosing Periods of 21 days, 0.035 mg)	Metabolism by CYP3A4	1.00 (0.96, 1.04)	1.04 (0.98, 1.10)
Albiglutide (5 Doses of 50 mg; Given Once Weekly on Days 7,14,21,28 and 35)	Simvastatin (80 mg, Dosing on Day 1 and on Day 38)	Metabolism by CYP3A4	**0.60 (0.52, 0.69)**	**1.18 (1.02, 1.38)**
	Simvastatin Acid		**1.36 1.19 1.55**	**1.98 (1.75, 2.25)**
Albiglutide (5 Doses of 50 mg; Given Once Weekly on Days 7,14,21,28 and 35)	Digoxin (0.5 mg; Dosing on Day 1 and Day 38)	Mainly renally excreted unchanged via P-gp transport	1.09 (1.01, 1.18)	**1.11 (0.98, 1.26)**
Albiglutide (5 Doses of 50 mg; Given Once Weekly on Days 14,21,28, 35 and 42)	Warfarin (25 mg; Dosing on Day 1 and Day 45)	Metabolism by CYP2C9 (*S*-warfarin)		
	S-Warfarin		0.99 (0.95, 1.03)	0.93 (0.87, 0.98)
	R-Warfarin	Metabolism by CYP1A2 and 3A4 (*R*-warfarin)	1.02 (0.98, 1.07)	0.94 (0.89, 0.99)

Bolded values indicate that the geometric mean ratio or 90 % CI is outside 80%-125% limit

2.6.6 What is the effect of albiglutide co-administration on the pharmacodynamics of other drugs?

There is no known mechanistic basis for pharmacodynamic drug-drug interactions for albiglutide with concomitant medications. However, albiglutide can delay the gastric emptying time which might impact pharmacokinetic of concomitant medications. Since warfarin and oral contraceptive are low therapeutic index drugs, minimal influences on their pharmacokinetics may have a significant impact on their pharmacodynamics.

Drug interaction studies with warfarin showed no changes in pharmacokinetics of S- and R-warfarin. Similar to the PK results, the PD of warfarin was not affected by co-administration of albiglutide. INR values after treatment with warfarin alone were essentially identical to from those seen after combination treatment with albiglutide and warfarin. The 90% CI for the ratio of INR_{max} and AUC(INR) between treatments fell within the usual equivalence interval from 0.80 to 1.25 (Table 17).

Table 17: Summary Statistical Analysis on INR parameters

Parameter (Unit)	Treatment	Geometric LS Means	Ratio of Geometric LS Means and 90% CI
INR_{AUC}	A	231.58	0.98 (0.96, 1.00)
	C	226.43	
INR_{max}	A	2.01	0.93 (0.89,0.97)
	C	1.86	

Treatments: A=Warfarin Alone, B=Warfarin with Albiglutide

2.6.7 What is the effect of injection site on the pharmacokinetics of albiglutide?

The effect of injection site on the pharmacokinetics of albiglutide was studies in an open-label, randomized, multi-site study. A single sc dose of 16 mg or 64 mg of albiglutide was administered by to one of three different sites (upper arm, thigh or abdomen) in subjects with T2DM and only at abdomen in healthy subjects.

In general, albiglutide exposures in T2DM were comparable following injection in the abdomen, upper arm and thigh (Figure 16). Table 18 provides summary of the key pharmacokinetics parameters. Albiglutide exposures were comparable following injection in the abdomen, arm and leg. Point estimates of geometric LSM ratios for AUC ranged from 1 to 1.08. Point estimates of the geometric LSM ratios for C_{max} ranges from 0.79 to 1.36 (Table 15).

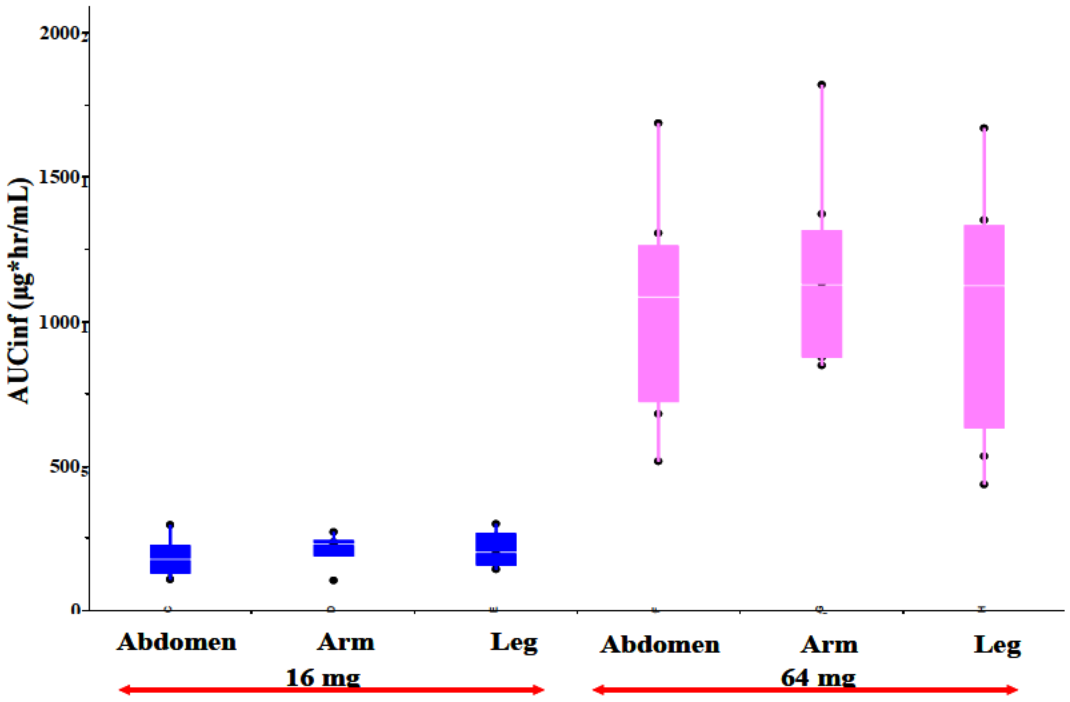


Figure 16: Exposure of Albiglutide Following Single SC Dose of 16 mg and 64 mg in Abdomen, Arm, and Leg.

Table 18: Summary of Selected Albiglutide Pharmacokinetic Parameters for by Treatment Group[1]

Treatment	AUC(0-7 days) (μg.hr/mL)	AUC(0-∞) (μg.hr/mL)	Cmax (ng/mL)	tmax (day)[2]	t1/2 (day)	CL/F (mL/hr)	V/F (L)
A	110 (16)	232 (24)	1080 (37)	3.84 (2.00, 7.83)	4.33 (36)	68.9 (24)	10.3 (36)
B	429 (23)	1030 (23)	3840 (22)	2.00 (2.00, 3.84)	5.33 (16)	62.0 (23)	11.4 (25)
C	52.4 (101)	175 (37)	614 (136)	3.95 (2.00, 7.84)	4.5 (28)	91.7 (37)	14.3 (26)
D	61.8 (99)	207 (36)	641 (70)	3.84 (2.75, 8.86)	4.13 (9)	77.3 (36)	11.1 (40)
	101 (39)	205 (29)	1010 (56)	3.84 (2.00, 4.00)	3.62 (19)	78.1 (29)	9.79 (40)
F	383 (53)	985 (39)	3550 (40)	3.86 (2.00, 8.86)	5.21 (10)	65.0 (39)	11.7 (36)
G	417 (22)	1120 (26)	3940 (23)	3.33 (1.99, 4.00)	5.67 (23)	57.4 (26)	11.3 (30)
H	374 (69)	972 (49)	3660 (54)	3.33 (2.00, 4.00)	5.29 (15)	65.9 (49)	12.1 (50)

1. geometric mean (CV%).
2. median (range)

A: 16 mg Abdomen – Healthy Volunteer, B: 64 mg Abdomen – Healthy Volunteer, C: 16 mg Abdomen – T2DM, D: 16 mg Upper Arm - T2DM, E: 16 mg Thigh – T2DM, F: 64 mg Abdomen – T2DM, G: 64 mg Upper Arm – T2DM, H: 64 mg Thigh – T2DM.

Table 19: Point estimates of Geometric LSM Ratios and 90%CIs for AUC and C_{max} following administration on Arm, Leg and Abdomen

Parameter	Dose (mg)	Geometric LSM of Abdomen	Geometric LSM of Test site	Comparison	Geometric LSM Ratio (90% CI)
AUC(0-∞) (ug.h/mL)	16	180.41	181.93	Arm vs Abdomen	1.01 (0.69 – 1.47)
		180.41	194.18	Leg vs Abdomen	1.08 (0.75 – 1.54)
	64	1024.08	1077.08	Arm vs Abdomen	1.05 (0.75 – 1.47)
		1024.08	1020.57	Leg vs Abdomen	1.00 (0.73 – 1.35)
Cmax (ng/mL)	16	663.74	522.14	Arm vs Abdomen	0.79 (0.43 – 1.45)
		663.74	899.53	Leg vs Abdomen	1.36 (0.77 – 2.38)
	64	3674.37	3810.08	Arm vs Abdomen	1.04 (0.59 – 1.83)
		3674.37	3761.72	Leg vs Abdomen	1.02 (0.61 – 1.72)

Reviewers Comment: In all the Phase 3 trials, the albiglutide was administered in abdomen only. To bridge the use of albiglutide in other injection site sponsor conducted this relative bioavailability study. Results from this study in summary indicate that albiglutide exposures were comparable following injection in the abdomen, upper arm and thigh. In T2DM subjects the geometric mean exposures were comparable among all three injection sites. Based on the study results albiglutide can be administered as a sc injection in different sites of injection without dose adjustment.

2.7 General Biopharmaceutics

An overview of the albiglutide drug products used in clinical trials is presented in Table 20 and Table 21.

During the clinical development of albiglutide, three manufacturing processes were used to produce albiglutide drug substance: Process 1, Process 2 and Process 3. Process 1 albiglutide drug substance was manufactured at a [(b) (4)] Process 2 drug substance [(b) (4)] Process 2 optimization resulted in approximatel [(b) (4)] compared to Process 1. The [(b) (4)] in Process 2 resulted in approximately [(b) (4)] than Process 1 in a [(b) (4)] Sponsor bridged the potency of Process 1 and Process 2 in nonclinical db/db mouse OGTT model. Please refer to pharmacology and toxicology review by Dr. Wange for further details. For commercialization, GSK improved the drug substance process including an [(b) (4)] This is referred to as Process 3.

Process 3 drug substances has been characterized and judged comparable analytically to Process 2 drug substance. Please refer to Chemistry Review by Dr. Pedras-Vasconcelos and Pharmacology and Toxicology review by Dr. Wange for further details. To clinically bridge the drug substance from Process 2 to Process 3 sponsor conducted a single dose BE study to compare PK between Process 2 and Process 3 drug substance.

Table 20: Clinical Trials and Albiglutide Products Used

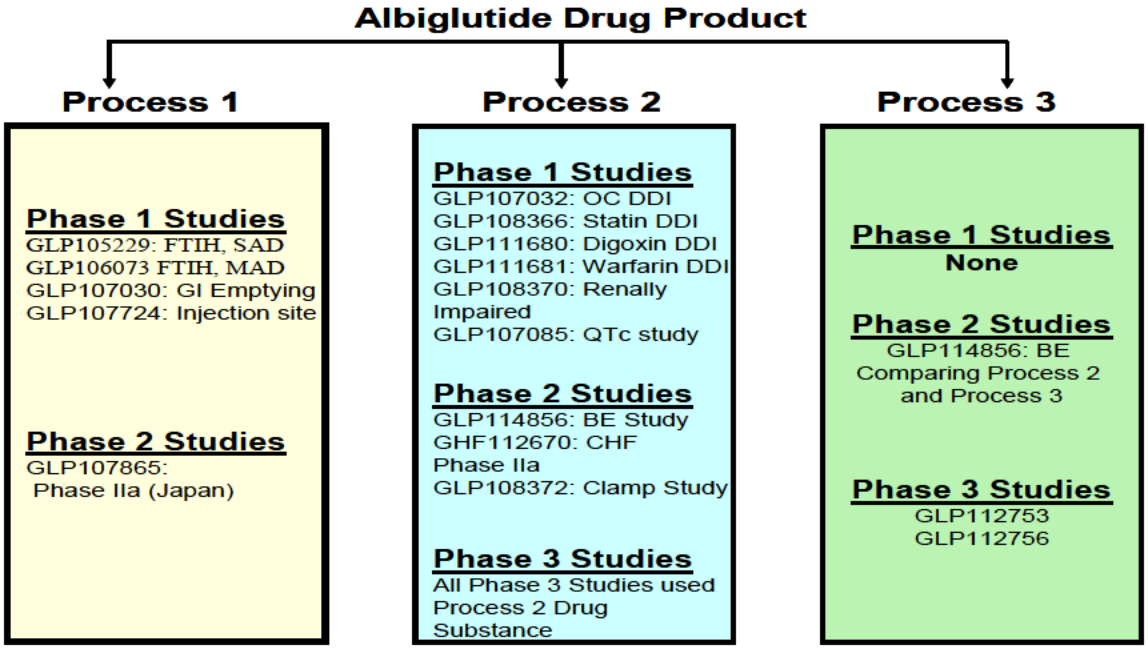


Table 21: Composition of the Albiglutide Products used in Clinical Trials

Albiglutide Drug Product: Process 1 Drug Substance

(b) (4)

Albiglutide Drug Product: Process 2 Drug Substance

(b) (4)

Albiglutide Drug Product: Process 3 Drug Substance

Drug Substance Process	Site of Manufacture	Formulation	Formulation Composition			Container Closure	Delivery System
			Component	Quantity			
				30 mg/DCC	50 mg/DCC		
Process 3	(b) (4)	10 mM phosphate 153 mM mannitol 117 mM trehalose 0.01% (w/w) polysorbate 80 pH 7.0	Albiglutide	40.30	66.95	DCC	pen injector
			Trehalose dihydrate	(b) (4)			
			Mannitol				
			(b) (4)				
			Sodium phosphate				
			(b) (4)				
			Polysorbate 80				
			Water for Injection	q.s. to 0.65 mL	q.s. to 0.65 mL		

Source: Sponsor report on Summary of Biopharmaceutics Studies and Associated Analytical Methods, pg: 11-13

2.7.1 Is bioequivalence established between the proposed commercial formulation and formulation used in Phase 2 and Phase 3 studies?

Yes sponsor conducted a single dose BE study and a multiple dose safety and efficacy study of 12 weeks (Study GLP114856) to bridge the drug substance from Process 2 (Phase 3 material) and Process 3 (to-be marketed material).

In all the Phase 3 studies and most of the Phase 1 and Phase 2 studies sponsor used drug substance from Process 2. To clinically bridge the drug substance from Process 2 to Process 3 sponsor conducted a single dose BE study to compare PK between Process 2 and Process 3 drug substance. In addition, sponsor conducted a multiple dose study to confirm that there are no clinically relevant differences between Process 2 and Process 3 in terms of efficacy, safety, tolerability, immunogenicity, and trough PK following weekly administration of 30 mg albiglutide from Process 2 or Process 3 for 12 weeks.

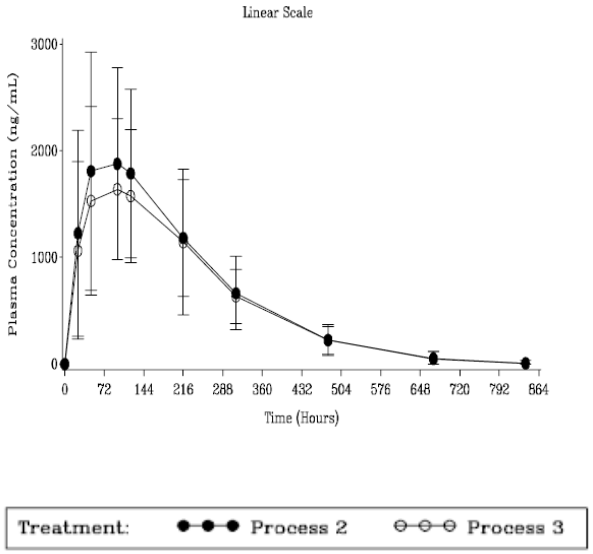
Study GLP114856 is a randomized, double-blind, multicenter 2 parallel-group study, in subjects with T2DM to show the clinical comparability of Process 2 and Process 3 drug products. This study has a single-dose (BE) phase that was used for the comparative PK assessment of Process 2 vs. Process 3 drug products. A multiple dose phase (Week 5 through Week 17) evaluated Process 2 and Process 3 drug products with regard to glycemic effect (e.g., HbA1c, fasting plasma glucose), immunogenicity, safety, and trough PK samples at Weeks 5, 9, 13, 17, and 25.

In addition to support the clinical comparability of Process 2 and Process 3 drug substance sponsor introduced Process 3 albiglutide into the extension phase of two ongoing Phase 3 clinical studies 1) GLP112754 (open-label insulin glargine comparison) and 2) GLP112756 (double-blind monotherapy study).

Single Dose BE Study:

The mean albiglutide plasma concentration-time plots are presented in Figure 17 following a single 30- mg dose administered subcutaneously. Albiglutide Process 3 is bioequivalent to albiglutide Process 2, with respect to AUC and C_{max}. The 90% confidence intervals of the ratios were completely within the criterion interval of 0.80 to 1.25 (Table 22).

Figure 17: Mean Plasma Concentration of Albiglutide Versus Time: BE Phase



Source: Sponsor's Summary of Biopharmaceutics Studies and Associated Analytical Methods

Table 22: Geometric Mean (%CV) Plasma Pharmacokinetic Parameters of Albiglutide: Bioequivalence Phase in Study GLP114856

Parameter (unit)	Albiglutide Process 2 (N=85) Mean (CV%)	Albiglutide Process 3 (N=80) Mean (CV%)
AUC(0-last) (hr•µg/mL)	447 (56)[1]	426 (45)
AUC(0-∞) (hr•µg/mL)	496 (42)[2]	465 (40)[3]
Cmax (µg/mL)	1.88 (58)	1.74 (49)
tmax (hr)[4]	95.50 (23.4, 214.3)	96.08 (20.5, 217.8)
t1/2 (hr)	106.4 (16)[2]	113.8 (23)[3]
tlag (hr)[4]	0.0 (0.0, 24.1)	0.0 (0.0, 24.1)
CL/F (mL/hr)	60.5 (41.8)[2]	64.5 (39.7)[3]
V/F (L)	9.28 (44.0)[2]	10.6 (44.3)[3]

Source Data: Study GLP114856 BE Phase Table 12 and Table BE14.4-1.2.

AUC(0-∞) = area under the plasma concentration-time curve from time 0 extrapolated to infinity, Cmax = maximum observed plasma concentration, tmax = time of occurrence of Cmax, t1/2 = terminal phase half-life, tlag = Lag time before observation of drug concentrations in sampled matrix.

Note: This table includes data for subjects enrolled under protocol amendment 1 only.

1. N=84.
2. N=75
3. N=74.
4. Median (minimum, maximum).

Source: Sponsor's Summary of Biopharmaceutics Studies and Associated Analytical Methods

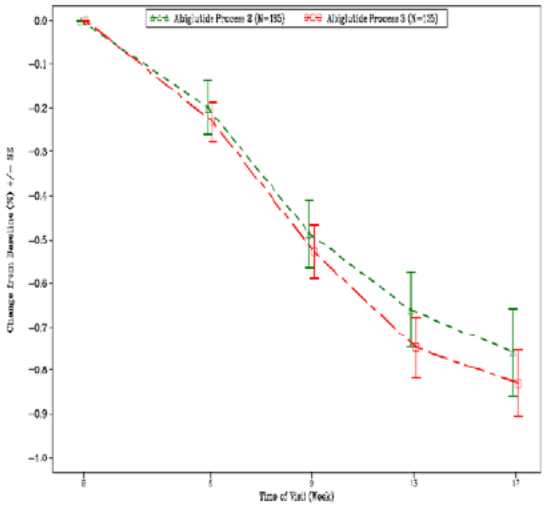
Multiple Dose Efficacy and Safety Study: The main efficacy objectives of the multiple dose study were to evaluate the effect of 30 mg of albiglutide (from Process 2 relative to Process 3) drug product administered weekly on change from baseline in HbA1c and FPG following 12 weeks of treatment.

In multiple dose study, a decrease in HbA1c from Baseline to Week 17 was observed in both treatment groups (Process 2 vs Process 3) and occurred in a similar manner (Figure 18). Change from Baseline in HbA1c at Week 17 was -0.75% and -0.84% for Process 2 and 3, respectively, and the mean treatment group difference of 0.08% was not statistically significant (p=0.4874).

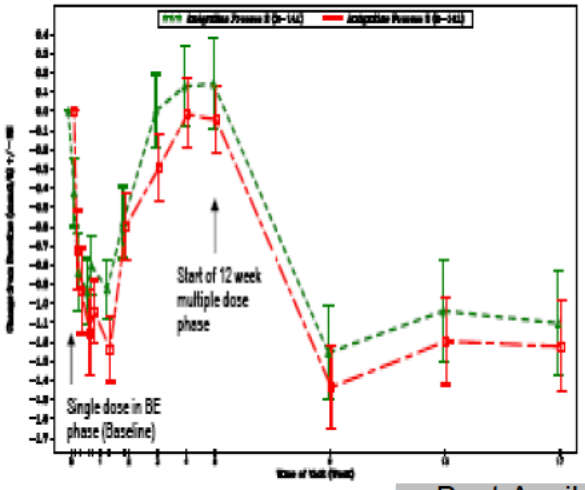
Changes from Baseline in FPG were consistent with those for HbA1c with a reduction of 1.10 mmol/L (-19.85 mg/dL) for Process 2 and a reduction of 1.22 mmol/L (-22.12 mg/dL) for Process 3. The mean treatment group difference of -0.10mmol/L (1.78mg/dL) was not statistically significant (p=0.7692).

Figure 18: Line Graph of Mean (±SE) Change From Baseline in A) HbA1c (%) B) Fasting Plasma Glucose (mmol/L) Over Time (Efficacy Population – LOCF)

A



B



Source: Sponsor's Study report for Study GLP114856 part 2. Page number 54-58

The overall safety profile (i.e., type and frequency of events reported) was similar between the Process 2 and Process 3 treatment groups. Please refer to Clinical Review by Dr. Vasisht for further details.

Reviewers Comment:
During the review cycle, GSK submitted an amended report on this pivotal BE study. This amended report included a post hoc sensitivity analysis excluding data from 6 subjects (Subjects 3520856997, 3524856981, 3524856984, 3524856986, 3524856987, and 3524856990), due to non-standard bioanalytical practice (GSK analysts re-analyzed sample runs until QC's passed without proper justification for the reanalysis). The results of the original statistical analysis is presented in* Table 23 *and the results of the revised statistical analysis after excluding subjects with non standard bioanalytical practice is presented in Table 24. Overall the revised statistical analysis showed no change in the conclusion of the study results.

In conclusion, the primary endpoint of bioequivalence between Process 2 and Process 3 albiglutide was achieved in the BE Phase of the study. In multiple dose phase, no clinically relevant differences between Process 2 and Process 3 with regards to efficacy parameters (i.e., HbA1c, FPG) was observed. Overall, these data suggest that albiglutide made by Process 3 is clinically comparable to that made by Process 2 in terms of efficacy. Please refer to Clinical review by Dr. Vasisht for further details on any safety related difference between Process 2 and Process 3 drug product.
In addition to this single dose and multiple dose study, sponsor switched the patients in two ongoing Phase 3 studies to receive Process 3 drug product. However, at the time of BLA submission the data following the switch from Process 2 to Process 3 is very limited to make any meaningful comparison on safety and efficacy.

Table 23: Statistical Analysis of Pharmacokinetic Parameters of Albiglutide: BE Phase (Albiglutide Pharmacokinetic Population)

Parameter	Treatment	n	Geometric LS Means	Ratio of Geometric LS Means (Process 3/Process 2)	90% CI of Ratio (Process 3/Process 2)
AUC(0-∞) (hr•ng/mL)	Process 2	75	496190		
	Process 3	74	464985	0.937	0.842, 1.042
Cmax (ng/mL)	Process 2	85	1881		
	Process 3	80	1743	0.927	0.813, 1.056

Source Data: Table BE14.4-1.3.
AUC(0-∞) = area under the plasma concentration-time curve from time 0 extrapolated to infinity, BE = bioequivalence, CI = confidence interval, Cmax = maximum observed plasma concentration, LS = least square.
Note: An analysis of variance was performed on natural logarithms of pharmacokinetic parameters. The model included treatment as a fixed effect.

Source: Sponsor's modified report on study GLP114856

Table 24: Statistical Analysis of Pharmacokinetic Parameters of Albiglutide: BE Phase Excluding Subjects with Non-standard Bioanalytical Practice (Albiglutide Pharmacokinetic Population)

Parameter	Treatment	n	Geometric LS Means	Ratio of Geometric LS Means (Process 3/Process 2)	90% CI of Ratio (Process 3/Process 2)
AUC(0-∞) (hr•ng/mL)	Process 2	74	494996.161	0.942	0.844 - 1.051
	Process 3	70	466320.313		
Cmax (ng/mL)	Process 2	83	1888.379	0.927	0.810 - 1.060
	Process 3	76	1749.903		

Source Data: Table BE14.4-1.3.1.

AUC(0-∞) = area under the plasma concentration-time curve from time 0 extrapolated to infinity, BE = bioequivalence, CI = confidence interval, Cmax = maximum observed plasma concentration, LS = least square.

Note: An analysis of variance was performed on natural logarithms of pharmacokinetic parameters. The model included treatment as a fixed effect. Subjects 3520856997, 3524856981, 3524856984, 3524856986, 3524856987, and 3524856990 were excluded from the analysis due to non-standard bioanalytical practice.

Source: Sponsor's modified report on study GLP114856

2.8 Analytical

2.8.1 How are the active moieties identified and measured in the plasma?

In this BLA, plasma concentrations of albiglutide were determined using two ELISA methods developed by (b) (4) and by GSK.

Albiglutide plasma concentrations were quantified in the (b) (4) method using an antibody capture sandwich ELISA with a colorimetric endpoint over a standard ranges of 10.0 to 320.0 ng/mL with the minimal dilution of 1:20. The methods were used to support the following Phase I clinical studies: GLP105229, GLP106073 and GLP107724.

In the GSK ELISA procedure, albiglutide plasma concentrations were quantified using an antibody capture sandwich ELISA with a chemiluminescent endpoint over a standard range of 50.0 to 1500.0 ng/mL with the minimal dilution of 1:100. The method was used to support the following Phase I, Phase II, and Phase III clinical studies: GLP107085, GLP107865, GLP108366, GLP108370, GLP110125, GLP110932, GLP112754, GLP112756, GLP112757, GLP114130, GLP114856, GLP107030, and GHF112670.

ELISA Method Developed by (b) (4)

The concentrations of albiglutide in human plasma were determined by an antibody capture sandwich ELISA. (b) (4) developed two different methods and the methods were variations on the same procedure. The only difference between the two methods was (b) (4)

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Table 25: Summary of Studies Analysed by GSK and the Time of Sample Analysis

Studies Analysed by GSK	Time of the Sample Analysis
GHF112670 (Phase 2a)	After July 2010
GLP107085 (QTc)	After July 2010
GLP114130(Phase 3 T2DM renal Impairment)	After July 2010
GLP114856 (Pivotal BE Study)	After July 2010
GLP110932 (Japan Phase 2)	After July 2010
GLP107865 (Phase 2 Japanese)	Before July 2010
GLP108370 (Phase 1 Renal)	Before July 2010
GLP110125 (Phase 2 b)	Before July 2010
GLP112754 (Phase 3)	Before July 2010
GLP107030 (Gastric Empyting)	Before July 2010
GLP112756 (Phase 3 Monotherapy)	Both Before and After
GLP112757 (Phase 3)	Both Before and After

3 DETAILED LABELING RECOMMENDATION

The following are the labeling recommendations relevant to clinical pharmacology for BLA 125431. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

5.7 Renal Impairment

In patients treated with other GLP-1 receptor agonists, there have been postmarketing reports of acute renal failure and worsening of chronic failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration.

7 DRUG INTERACTIONS

(b) (4) causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. (b) (4) caution should be exercised when oral medications are concomitantly administered with (b) (4) *see Clinical Pharmacology (12.3)]*.

Reviewers Comment: The text above is added to make it consistent with liraglutide product label.

8.6 Renal Impairment

(b) (4)

(b) (4)

(b) (4)

12.2 Pharmacodynamics

(b) (4)

Reviewers Comment: (b) (4)

(b) (4)

Reviewers Comment: The results of the QT study are described separately under section 12.6 Cardiac Electrophysiology.

12.3 Pharmacokinetics

Absorption: (b) (4)

Following SC administration of a single 30 mg dose to subjects with type 2 diabetes, maximum concentrations of albiglutide were reached at 3 to 5 days post dosing (b) (4) The mean peak (C_{max}) and mean area under the time-concentration curve (AUC) of albiglutide were 1.74 mcg/mL and 465 mcg•h/mL, respectively, following a subcutaneous single dose of 30 mg in type 2 diabetic subjects.

(b) (4)

(b) (4)

Steady-state exposures are achieved following 4 to 5 weeks of once-weekly administration. Exposures at the 30 mg and 50 mg dose levels were consistent with a dose-proportional increase. Similar exposure is achieved with SC administration of albiglutide in the abdomen, thigh, or upper arm. The absolute bioavailability of albiglutide following SC administration has not been evaluated.

Specific (b) (4) Patient Populations:

Age, Gender, Body weight and Race: Based on population pharmacokinetic analysis with data collected from 1113 subjects, age, gender, body weight and race do not have a clinically relevant effect on the pharmacokinetics of albiglutide.

(b) (4)

Pediatric: No pharmacokinetic data are available in pediatric patients.

Renal: In a population pharmacokinetic analysis including a Phase III trial in patients with mild, moderate and severe renal impairment, exposures were increased by approximately 30 to 40% in severe renal impairment compared to those observed in type 2 diabetic patients with normal renal function. (b) (4)

Hepatic: No clinical trials were conducted to examine the effects of mild, moderate, or severe hepatic impairment on the pharmacokinetics of albiglutide. Therapeutic proteins such as albiglutide are catabolized by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of albiglutide.

(b) (4)

4 APPENDIX

(b) (4)

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03/04/2013

LOKESH JAIN
03/04/2013

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4.3 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	BLA 125431
Submission Date(s)	1/14/2013; 3/7/2013; 6/17/2013
Compound	Albiglutide injection
Dosing regimen	30 mg subcutaneously once weekly. The dose may be increased to 50 mg once weekly based on individual glycemic response.
Indication	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Clinical Division	DMEP
Pharmacometrics Reviewer (s)	Jayabharathi Vaidyanathan, Ph.D., Anshu Marathe, Ph.D.
Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

1.1.1 Is there dose-response for effectiveness endpoints?

Yes, there is evidence of dose-response relationship for mean change from baseline in HbA1c in type 2 diabetes patients in Phase 3 study GLP112756. Patients were randomized to either receive albiglutide 30 mg without uptitration or to receive albiglutide 30 mg followed by uptitration to 50 mg at week 12 (forced titration) in GLP112756. The time-profiles for the mean change from baseline in HbA1c in GLP112756 are shown in Figure 1. There is a larger decline in HbA1c with increased dose of 50 mg weekly compared to 30 mg weekly. GLP112756 is the only Phase 3 trial that provides information regarding the dose-response relationship of albiglutide. In other Phase 3 trials uptitration from 30 mg to 50 mg albiglutide occurred because of insufficient glycemic control with albiglutide 30 mg (optional uptitration following a protocol-specific algorithm).

Dose response was also observed in the weekly dosing regimen group of the Phase 2 study, GLP 110125. The mean change in HbA1c from baseline at week 16 were -0.11, -0.49 and -0.87 respectively for the 4 mg, 15 mg and 30 mg weekly doses. It should be noted that the 50 mg weekly dose was not studied in the Phase 2 study (Figure 2).

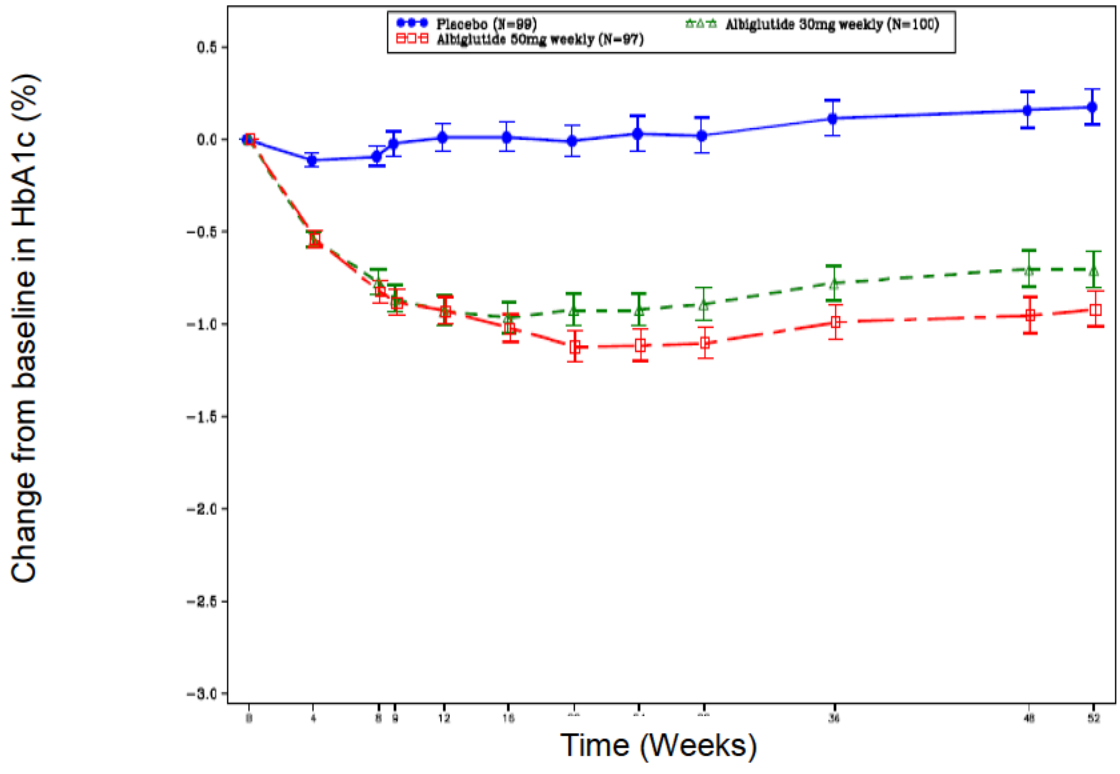


Figure 1: Time profiles for mean change from baseline in HbA1c in GLP 112756 upon administration of placebo (blue), 30 mg weekly (green) and 50 mg weekly (red) doses of albiglutide. Source: Figure 3 of sponsor's study report.

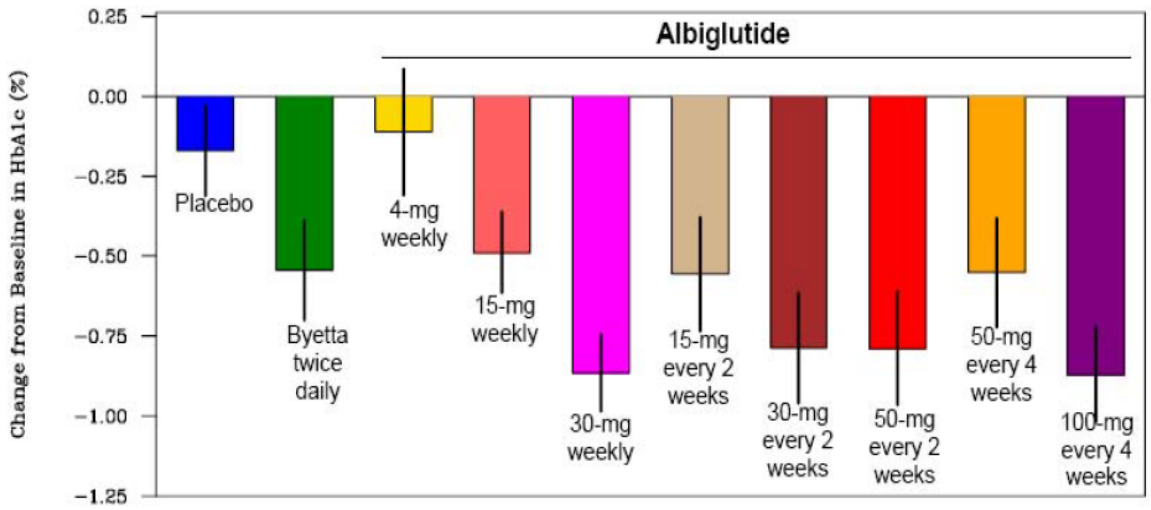


Figure 2: Mean (+/- SE) change from baseline in HbA1c at week 16 in GLP 110125
Source: Figure 1of sponsor's study report

1.1.2 Is there dose-response for safety endpoints?

Phase 3 study, GLP112756 (with a forced titration design) indicated no clear dose response relationship for safety endpoints. There was no clear dose response relationship identified in phase 3 trials where optional uptitration was employed (Studies GLP108486, GLP112753, GLP112754, and GLP112757). There was increase in GI related adverse events (nausea and vomiting) with dose in Phase 2 study, GLP 110125.

Since GLP112756 had a forced titration design, there are three analyses directed at dose response in this study by the sponsor.

- First, the overall data was compared between dosing arms.
- Second, because many events in the 50 mg arm occurred while subjects were still on 30 mg (ie. first 12 weeks), an analysis comparing the pre- and post-titration period in the 50 mg arm was undertaken.
- Finally, the treatment arms were compared in the post-titration period (Weeks 12-52). The totality of these assessments was necessary to complete the dose response assessment.

The analyses focus on both proportion of patients with adverse events and the density of these adverse events. Density per 100 person-years is defined as 100 * number of AEs /person-years where person-years is the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the treatment period. A comparison of density was important to account for differences in treatment duration of the treatment groups. There was an increase in the proportion of patients with injection site reactions, sinusitis and pain in extremity with dose. The density of these adverse events (AEs) also increased with increasing dose (Table 1).

However for these AEs the density is lower in the post titration phase compared to the pre-titration phase (Table 2). Thus no clear dose-response relationship for adverse events could be identified in GLP112756.

In the phase 3 trials where optional uptitration was employed (Studies GLP108486, GLP112753, GLP112754, and GLP112757), among common AEs (sinusitis, nausea, vomiting, back pain, cough, diabetic retinopathy and hypertension) all had higher proportion and AE incidence in the 50 mg overall group compared to 30 mg group. However, with the exception of diabetic retinopathy, the proportion and AE densities for those AEs were lower post-titration than pre-titration (data not shown). The pre-titration event rate for diabetic retinopathy was 1.62 AEs/100 person years, while the post-titration rate was 3.27 AEs/100 person years. However, since diabetic retinopathy is closely associated with the disease state, it is unclear that this increase in diabetic retinopathy in the 50 mg dose group is due to increase in drug exposure or due to the severity of disease in these patients who required higher albiglutide dose for glycemic control. For injection site reactions, there was a lower proportion of subjects and AE density in 50 mg (14.3%, 54.66/100 person years) compared to the 30 mg (15.9%. 56.92/100 person years). Within the 50 mg arm, the proportion of subjects having an injection site reaction and the event density was lower in the post titration period (8.2%, 44.48/100 person years) compared to the pre-titration period (8.8%, 77.60/100 person years). This supports the conclusion from the GLP112756 study that there is not a clinically relevant dose response with regard to injection site reaction.

In the phase 2 study GLP11025, an increase in nausea and vomiting was observed with increasing dose. The proportion of patients with nausea was 14.3%, 20% and 25.8% at the 4 mg, 15 mg and 30 mg weekly dosing regimen (Table 3). The proportion of patients with vomiting was 0%, 8.6% and 12.9% at the 4 mg, 15 mg and 30 mg weekly dosing regimen (Table 3).

Table 1: On Therapy Adverse Events by Treatment Arms in GLP 112756

	Placebo (N=101)		Albiglutide 30 mg weekly (N=101)		Albiglutide 50 mg weekly (N=99)	
	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]
Any on-therapy event	82 (81.2)	569/284.26	85 (84.2)	644/294.26	86 (86.9)	535/279.88
Infections and Infestations						
Any Event	55 (54.5)	104/51.96	53 (52.5)	95/43.41	47 (47.5)	112/58.59
Upper respiratory tract infection	16 (15.8)	22/10.99	11 (10.9)	12/5.48	16 (16.2)	19/9.94
Nasopharyngitis	6 (5.9)	9/4.50	8 (7.9)	11/5.03	7 (7.1)	8/4.19
Bronchitis	8 (7.9)	11/5.50	7 (6.9)	8/3.66	7 (7.1)	8/4.19
Sinusitis	6 (5.9)	7/3.50	6 (5.9)	6/2.74	7 (7.1)	10/5.23
Influenza	3 (3.0)	3/1.50	7 (6.9)	11/5.03	5 (5.1)	6/3.14
Urinary tract infection	6 (5.9)	11/5.50	2 (2.0)	2/0.91	7 (7.1)	11/5.75
Cellulitis	2 (2.0)	2/1.00	7 (6.9)	7/3.20	2 (2.0)	3/1.57

	Placebo (N=101)		Albiglutide 30 mg weekly (N=101)		Albiglutide 50 mg weekly (N=99)	
	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]	n (%)	Number of AEs/Density[1]
Pharyngitis	6 (5.9)	9/4.50	3 (3.0)	4/1.83	3 (3.0)	6/3.14
Gastrointestinal disorders						
Any event	36 (35.6)	70/34.97	41 (40.6)	77/35.18	34 (34.3)	68/35.57
Diarrhoea	15 (14.9)	20/9.99	12 (11.9)	19/8.68	15 (15.2)	19/9.94
Nausea	10 (9.9)	10/5.00	14 (13.9)	16/7.31	10 (10.1)	16/8.37
Gastroesophageal reflux disease	2 (2.0)	4/2.00	2 (2.0)	2/0.91	5 (5.1)	5/2.62
Abdominal pain	8 (7.9)	8/4.00	4 (4.0)	4/1.83	2 (2.0)	2/1.05
Dyspepsia	6 (5.9)	6/3.00	4 (4.0)	5/2.28	2 (2.0)	2/1.05
General disorders and administration site conditions						
Any event	22 (21.8)	68/33.97	32 (31.7)	121/55.29	37 (37.4)	115/60.16
Injection site reaction	2 (2.0)	30/14.99	10 (9.9)	42/19.19	18 (18.2)	71/37.14
Fatigue	5 (5.0)	6/3.00	7 (6.9)	7/3.20	4 (4.0)	4/2.09
Chest Pain	5 (5.0)	6/3.00	5 (5.0)	5/2.28	1 (1.0)	1/0.52
Injection site haematoma	5 (5.0)	11/5.50	1 (1.0)	1/0.46	2 (2.0)	2/1.05
Musculoskeletal and connective tissue disorders						
Any event	29 (28.7)	52/25.98	34 (33.7)	66/30.16	24 (24.2)	40/20.93
Back pain	6 (5.9)	7/3.50	8 (7.9)	8/3.66	5 (5.1)	5/2.62
Pain in extremity	3 (3.0)	3/1.50	6 (5.9)	6/2.74	7 (7.1)	7/3.66
Arthralgia	6 (5.9)	9/4.50	6 (5.9)	11/5.03	4 (4.0)	9/4.71

Source: Table 61 of sponsor's summary of clinical safety

Table 2: Ontherapy Adverse Events Occurring in Treated Subjects in the Uptitration Group Before and After Titration in GLP112756

	Albiglutide 50 mg weekly (N=99)			
	Before Titration[1]		After Titration[1]	
	n (%)	Number of AEs/Density[2]	n (%)	Number of AEs/Density[2]
Any ontherapy event	53 (53.5)	121/488.62	73 (73.7)	414/248.81
Infections and Infestations				
Any Event	17 (17.2)	22/88.84	41 (41.4)	90/54.09
Upper respiratory tract infection	2 (2.0)	3/12.11	14 (14.1)	16/9.62
Nasopharyngitis	1 (1.0)	1/4.04	6 (6.1)	7/4.21
Bronchitis	0	0	7 (7.1)	8/4.81
Sinusitis	2 (2.0)	2/8.08	6 (6.1)	8/4.81
Urinary tract infection	2 (2.0)	3/12.11	6 (6.1)	8/4.81
Gastrointestinal disorders				
Any event	14 (14.1)	20/80.76	28 (28.3)	48/28.85
Diarrhoea	7 (7.1)	7/28.27	10 (10.1)	12/7.21
Nausea	4 (4.0)	4/16.15	8 (8.1)	12/7.21
General disorders and administration site conditions				
Any event	12 (12.1)	20/80.76	27 (27.3)	95/57.09
Injection site reaction	3 (3.0)	10/40.38	15 (15.2)	61/36.66
Musculoskeletal and connective tissue disorders				
Any event	6 (6.1)	10/40.38	19 (19.2)	30/18.03
Back pain	1 (1.0)	1/4.04	4 (4.0)	4/2.40
Pain in extremity	1 (1.0)	1/4.04	6 (6.1)	6/3.61
Nervous system disorders				
Any event	5 (5.1)	5/20.19	17 (17.2)	25/15.02
Headache	2 (2.0)	2/8.08	7 (7.1)	11/6.61
Respiratory, thoracic, and mediastinal disorders				
Any event	5 (5.1)	5/20.19	12 (12.1)	20/12.02
Cough	1 (1.0)	1/4.04	6 (6.1)	7/4.21
Vascular disorders				
Any event	2 (2.0)	2/8.08	11 (11.1)	11/6.61
Hypertension	1 (1.0)	1/4.04	8 (8.1)	8/4.81

Source: Table 62 of sponsor's summary of clinical safety

Table 3: Most Common Ontherapy Adverse Events in GLP110125

			Albiglutide								
Preferred Term (n, %)	Placebo (N=51)	Byetta twice-daily (N=35)	4-mg weekly (N=35)	15-mg weekly (N=35)	30-mg weekly (N=31)	15-mg every other week (N=33)	30-mg every other week (N=32)	50-mg every other week (N=35)	50-mg every 4 weeks (N=35)	100-mg every 4 weeks (N=34)	Total Subjects
Nausea	6 (11.8)	14 (40.0)	5 (14.3)	7 (20.0)	8 (25.8)	9 (27.3)	8 (25.0)	19 (54.3)	13 (37.1)	18 (52.9)	107
Headache	3 (5.9)	4 (11.4)	6 (17.1)	5 (14.3)	5 (16.1)	6 (18.2)	5 (15.6)	4 (11.4)	5 (14.3)	8 (23.5)	51
Vomiting	1 (2.0)	6 (17.1)	0	3 (8.6)	4 (12.9)	3 (9.1)	3 (9.4)	10 (28.6)	6 (17.1)	14 (41.2)	50
Diarrhea	2 (3.9)	8 (22.9)	5 (14.3)	2 (5.7)	5 (16.1)	4 (12.1)	7 (21.9)	6 (17.1)	6 (17.1)	7 (20.6)	52
Hyperglycaemia[a]	7 (13.7)	0	6 (17.1)	2 (5.7)	2 (6.5)	4 (12.1)	4 (12.5)	4 (11.4)	1 (2.9)	4 (11.8)	34
Nasopharyngitis	3 (5.9)	2 (5.7)	2 (5.7)	4 (11.4)	3 (9.7)	2 (6.1)	3 (9.4)	4 (11.4)	4 (11.4)	2 (5.9)	29
Dizziness	4 (7.8)	3 (8.6)	5 (14.3)	2 (5.7)	2 (6.5)	2 (6.1)	2 (6.3)	2 (5.7)	5 (14.3)	2 (5.9)	29
Back pain	3 (5.9)	0	5 (14.3)	2 (5.7)	2 (6.5)	2 (6.1)	2 (6.3)	2 (5.7)	2 (5.7)	2 (5.9)	22
Upper respiratory tract infection	5 (9.8)	4 (11.4)	3 (8.6)	0	3 (9.7)	5 (15.2)	2 (6.3)	1 (2.9)	3 (8.6)	0	26
Influenza	0	0	1 (2.9)	0	3 (9.7)	3 (9.1)	2 (6.3)	3 (8.6)	3 (8.6)	0	15

Data Source: Table 14.3.1-4.1

Note: On-therapy events are those that have a start date on or after the first day of study drug administration and within 56 days after the end of study drug administration.

a. Events of hyperglycaemic rescue that prompted early termination of study drug were captured on the AE page of the CRF. However, because these events were a study endpoint (lack of efficacy), they should not have been captured as AEs and should not have been included in this table. See Section 7.2.12.

Source: Table 18 of sponsor's clinical study report

1.1.3 Is the proposed dosing scheme of 30 mg once weekly with uptitration to 50 mg weekly based on individual glycemic response reasonable?

The proposed dosing scheme of 30 mg once weekly with uptitration to 50 mg weekly based on individual glycemic appears reasonable because:

- There is an increase in mean change from baseline in HbA1c in 50 mg dose group compared to 30 mg dose group in forced titration study GLP 112756 (Figure 1, section 1.1.1)
- There was improvement in response (HbA1c) in patients after dose titration in optional up-titration studies. Figure 3 shows mean change from baseline in HbA1c for subjects requiring uptitration of albiglutide in each of the 4 studies which allowed optional uptitration. The data for each of the 4 studies show an initial rapid drop in HbA1c. For these subjects, however, there was a return of hyperglycemia which resulted in the uptitration of their albiglutide dose from 30 mg weekly to 50 mg weekly. The vertical dashed line indicates the last HbA1c value along the relative time scale prior to uptitration of the dose. The data after this uptitration line indicate a restoration of HbA1c to levels seen with the initial 30-mg dose regimen.
- There is no clear dose response relationship for safety endpoints identified in GLP 112756 (section 1.1.2).
- There is no clear dose response relationship for safety endpoints identified in optional uptitration studies except for diabetic retinopathy (section 1.1.2).

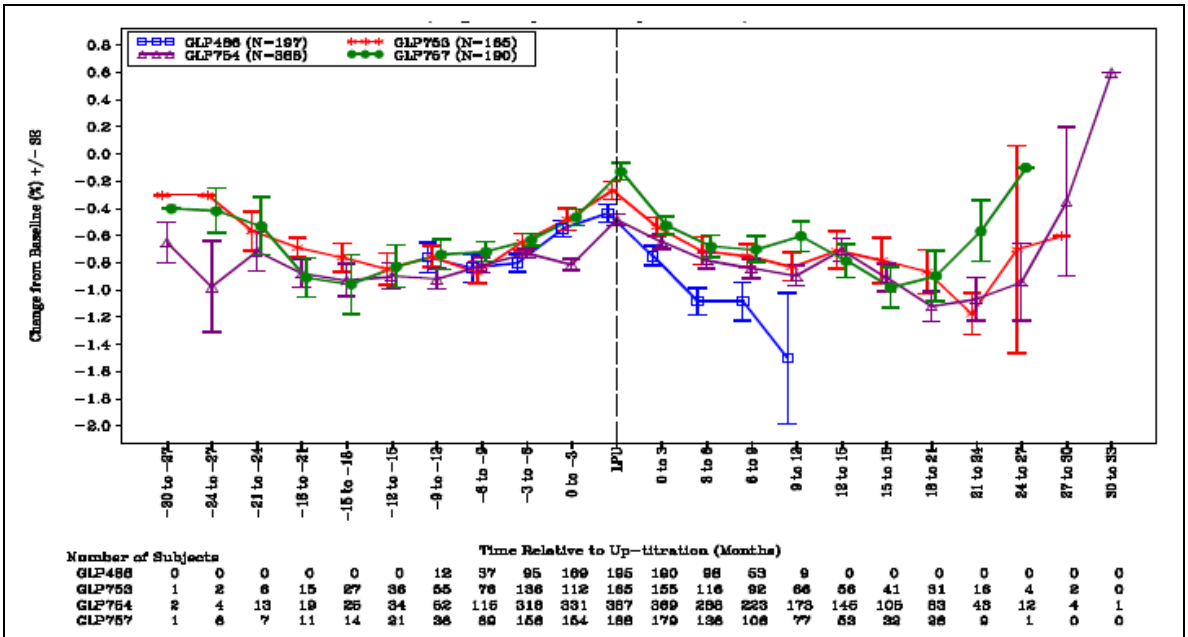


Figure 3: Mean change from baseline in HbA1c (%) relative to time of uptitration excluding post rescue values. Source: Figure 21 of Sponsor's Summary of Clinical Efficacy.

1.1.4 Is the proposed dosing recommendation regarding missed dose and changing the day of weekly administration acceptable?

The proposed package insert has the following statement "If a dose is missed, (b) (4) administered as soon as possible within 3 days after the missed dose. Thereafter, patients can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, patients should wait until their next regularly scheduled weekly dose. The day of weekly administration may be changed if necessary as long as the last dose was administered 4 or more days before."

In response to Agency information request, the sponsor submitted PK/PD simulations of various scenarios including missing a dose at steady-state, late dose at steady-state or change in day in the weekly dosing schedule of albiglutide. All these simulations indicate that potential changes in albiglutide steady-state concentrations do not result in significant changes in the HbA1c or FPG (Figure 4, Figure 5 and Figure 6). Therefore, the proposed dosing recommendations are acceptable.

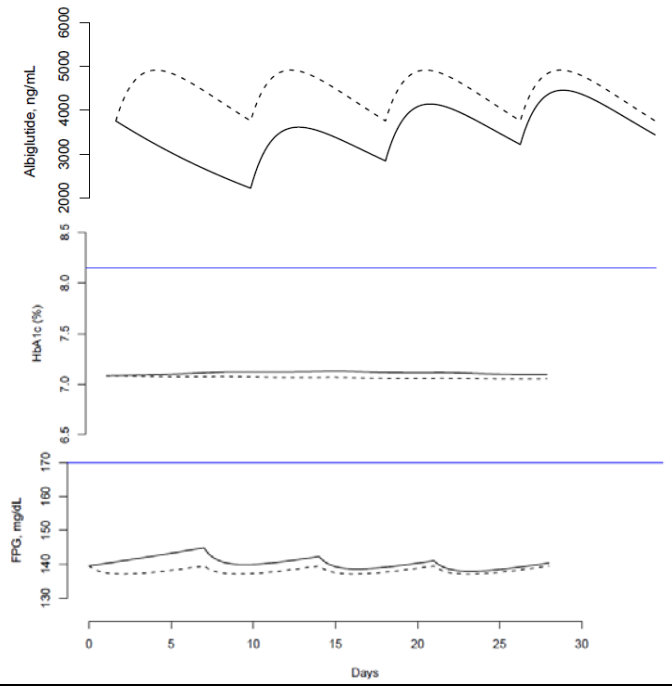


Figure 4: Mean albiglutide PK/PD profile simulations following a missed dose at steady-state. Source: Sponsor's Efficacy Information Amendment, page 3. The broken line represents the profile of PK or PD of albiglutide 50mg taken according to a once weekly schedule at steady-state. The solid line represents a missed dose on Day 0 with the subsequent doses taken on the usual once weekly schedule. The blue lines represent the model predicted baseline values for HbA1c and FPG.

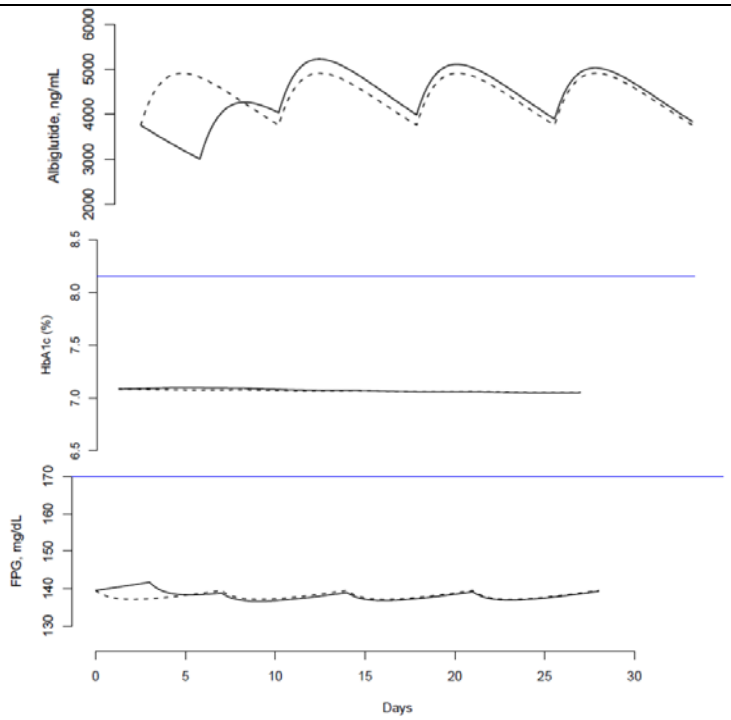


Figure 5: Mean albiglutide PK/PD profile simulations for taking a dose 3 days late at steady-state. Source: Sponsor's Efficacy Information Amendment, page 5. The broken line represents the profile of PK or PD of albiglutide 50mg taken according to a once weekly schedule at steady-state. The solid line represents a 50mg dose taken 3 days late (Day 3) with the subsequent doses taken according to the once weekly schedule. The blue lines represent the model predicted baseline values for HbA1c and FPG.

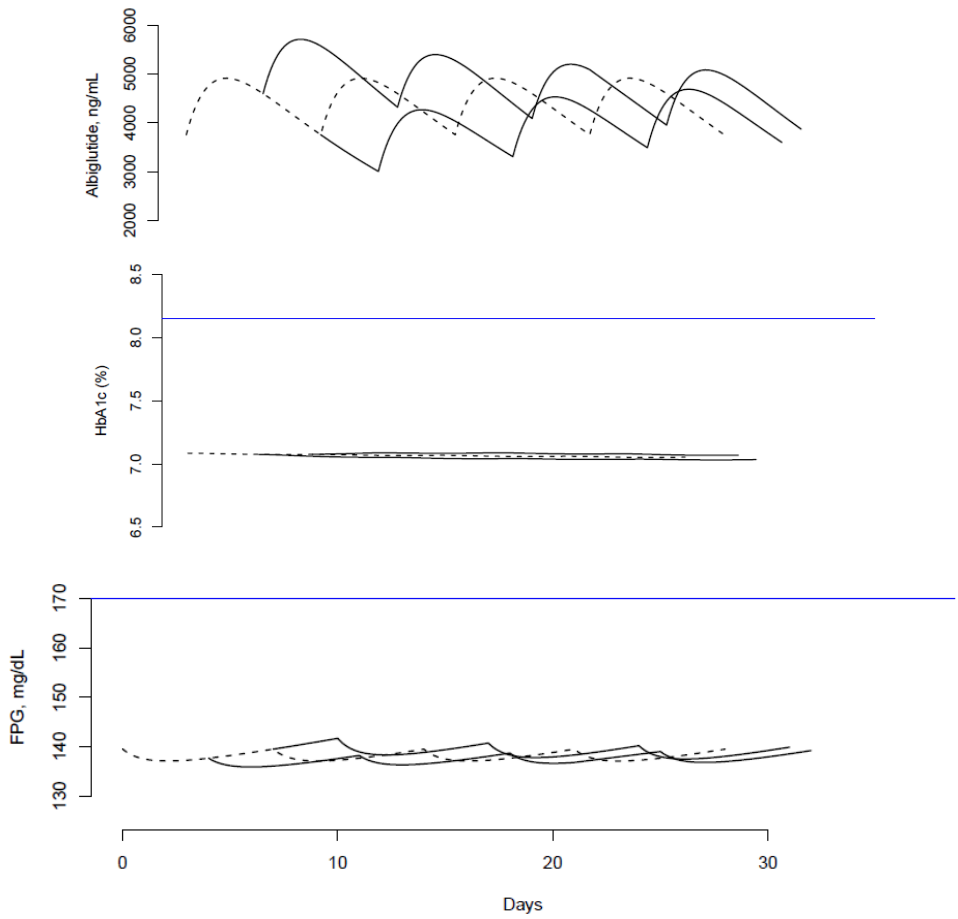


Figure 6: Mean albiglutide PK/PD profile simulations for changing the day of weekly administrations at steady-state. Source: Sponsor's Efficacy Information Amendment, page 6. The broken line represents the profile of each PK or PD of albiglutide 50mg taken according to a once weekly schedule at steady-state. The two solid line represents a 50mg dose taken either 4 days following the previous dose (Day 4), or 10 days following the previous dose with subsequent doses taken every 7 days. The blue lines represent the model predicted baseline values for HbA1c and FPG.

1.2 Recommendations

Division of Pharmacometrics has reviewed and finds BLA 125431 acceptable from a clinical pharmacology perspective and recommends approval.

1.3 Labeling Recommendations

The following are the labeling recommendations relevant to clinical pharmacology for BLA 125431 that were based on population PK analysis. The ~~red strikeout font~~ is used to

show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

12.3 Pharmacokinetics

Elimination:

The mean apparent clearance of albiglutide is 67 mL/h with an elimination half-life of approximately 5 days, making albiglutide suitable for once-weekly administration.

(b) (4) Specific Patient Populations:

Effects of Age, Gender, Body weight and Race:

Based on population pharmacokinetic analysis with data collected from 1113 subjects, age, gender, body weight and race (b) (4) *clinically relevant effect on the pharmacokinetics of albiglutide.*

(b) (4)

Renal: In a population pharmacokinetic analysis including a Phase III trial in patients with mild, moderate and severe renal impairment, exposures were increased by approximately 30 to 40% in severe renal impairment compared to those observed in type 2 diabetic patients with normal renal function. (b) (4)

Reviewer's comments:

- *Proposed labeling claim by the sponsor that "there is no clinically meaningful effect of age, gender, body weight and race on albiglutide pharmacokinetics" is acceptable because*
    - Inclusion of all covariates (body weight, race, eGFR and use of insulin use) accounted for only 7.5% of inter-individual variability of CL/F (i.e., decrease in inter-individual variability from 42.4% to 34.9%).
    - While body weight is identified as a covariate in the population PK model, there is not a strong correlation between clearance and body weight and there is considerable variability in the data as seen in Figure 7B. Over the ranges of body weight observed in this study, the mean estimate of CL/F in

the lowest body weight (44.3 kg) is 0.51-fold of the average CL/F and for the highest body weight (157.7 kg), it is 1.67-fold of the average CL/F. Similarly no significant effect of age and gender is seen on clearance (Figure 7 A and D). Additionally similar efficacy of the drug was observed in Phase 3 studies across baseline BMI categories (data not shown). The proportion of subjects who experienced ontherapy AE tended to increase as baseline BMI increased (for details see sponsor's integrated safety report). This is unlikely exposure related because based on the trend of clearance and body weight it is expected that patients with higher BMI would have lower exposures.

- There is 28% decrease in clearance in patients with severe renal impairment compared to normal patients. This corresponds to a 39% increase in exposure in patients with normal renal function compared to normal patients. For further details on the effect of renal impairment on efficacy and safety of the drug, see Clinical Pharmacology review.
- There is less than 25% decrease in clearance in patients of other races compared to Whites (Figure 7).

- *The details of the* [redacted] (b) (4) *have been removed to keep the label concise.*
- *Proposed labeling claim by the sponsor that "the apparent clearance of albiglutide is 67 mL/h" is acceptable based on the review of sponsor's final population PK model*
- [redacted] (b) (4)

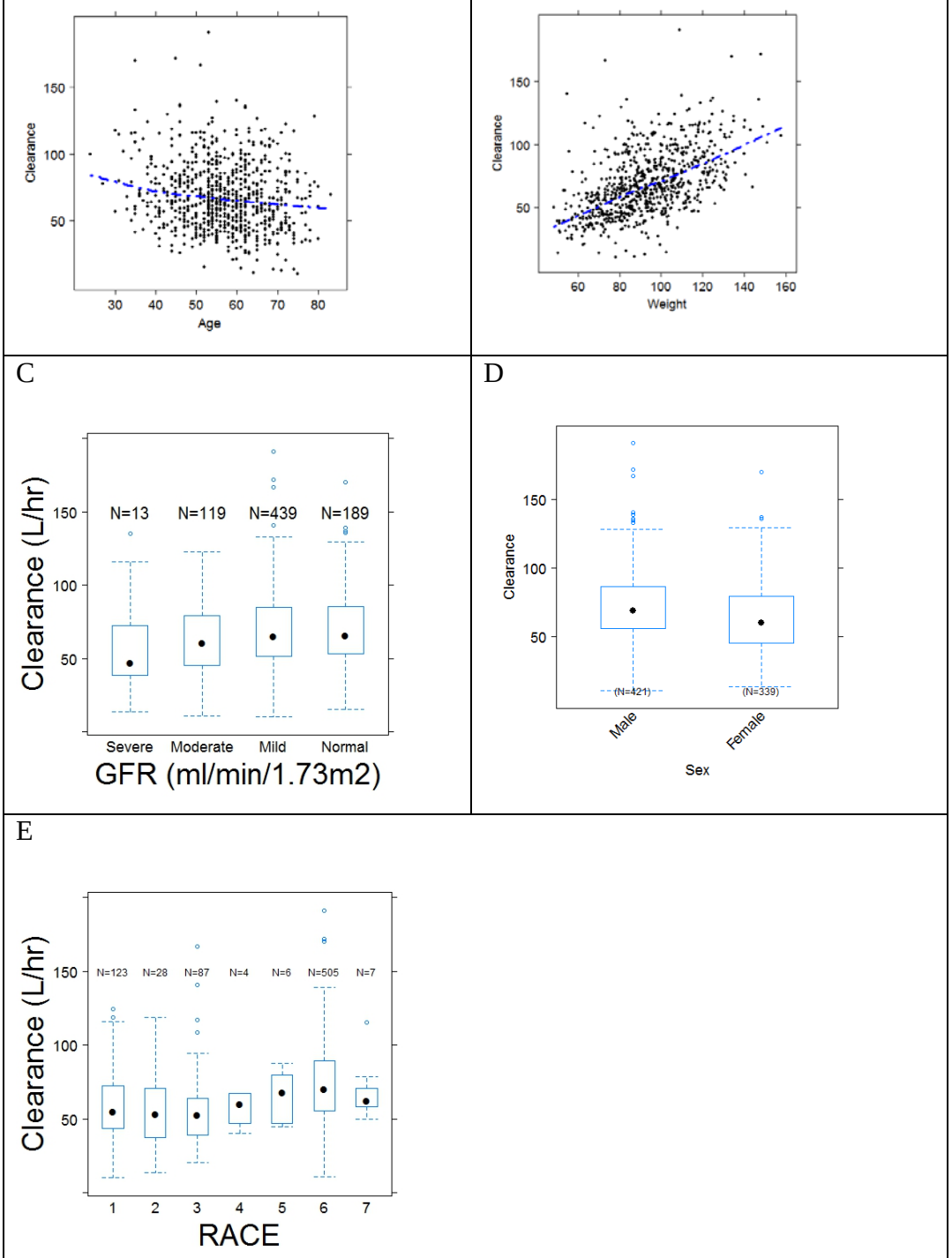


Figure 7: Effect of covariates on clearance. Scatter plot of A) CL versus age and B) CL versus weight. Box plot of C) CL versus renal impairment group D) CL versus gender and E) CL versus RACE. The race categories are 1= African America, 2= American Indian, 3=Asian, 4=Native Hawaiian or Pacific Islander, 5= Arabic/North African heritage, 6= Caucasian and 7 =Others.

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK Analysis

The population PK analysis for albiglutide was performed using data obtained from four Phase 3 clinical trials (protocol numbers GLP112754, GLP112756, GLP112757, and GLP114130). All data used in PK analysis were obtained from subjects with type 2 diabetes mellitus enrolled in these trials and received albiglutide either alone or in combination with other antidiabetic medications. Primary objective of the population PK analysis was to:

- Characterize the population PK of albiglutide in patients with type 2 diabetes mellitus (T2DM)
- Identify covariates (age, race, gender, renal function, body weight etc.) that have a significant effect on PK

2.1.1 Methods

In trials, GLP112754, GLP112757 and GLP112756, PK sampling was done at Week 8 and Week 24 at pre-dose. In addition, a PK sample was obtained at Week 9 (postdose PK sampling may be performed any time between Weeks 8 and 10, at least 2 days after administration of a dose) and at Week 28 (postdose PK sampling may be performed any time between Weeks 24 and 28, at least 2 days after administration of a dose)

In GLP114130, PK samples were obtained at Weeks 8 and 16 at predose and at Week 9 and Week 20, post dose (The Week 9 postdose PK sampling may be performed any time between Weeks 8 and 10, at least 2 days after administration of a dose; Week 20 postdose PK sampling may be performed any time between Weeks 16 and 20, at least 2 days after administration of a dose).
A total of 1113 subjects who received albiglutide were included in the PK analysis. All PK samples were analyzed using an enzyme linked immunosorbent assay (ELISA). Albiglutide concentrations, demographic information, and selected physiological measures were used to build NONMEM input data for PK analysis. The observed upward shift in albiglutide concentrations in blood samples assayed at later times was accounted for by inclusion of assay flags in NONMEM input data. The population PK analysis was performed and individual post hoc predicted PK parameters were obtained.

A sequential modeling approach was used to assess the PK of albiglutide. Population PK and PK/PD analyses were carried out using NONMEM (Version 7.1.2), PDx-Pop (Version 4.20) and Intel Visual Fortran Compiler (Version 12) on Microsoft Windows XP Professional.

2.1.2 Final Model

A one-compartment PK model with first order absorption and elimination processes was selected to describe PK of albiglutide.

The covariate analysis for the PK model was performed using the full covariate model approach. The full covariate model included the following covariates for CL/F: body weight, age, eGFR, sex, race (African American/African heritage), antidiabetic and nonantidiabetic concomitant medications (metformin, sulfonylureas, ACE inhibitors, angiotensin receptor blockers, beta blockers, calcium-channel blockers, hydrochlorothiazides, insulin, thiazolidinediones). Each individual race was included in the initial covariate analysis. Due to the model minimization problem and the fact that the number of subjects in most races was low, the decision was made by the sponsor that only African American/African heritage racial group versus the other races was to be included in the full covariate and the final PK models. The final PK model was reached with body weight, eGFR, race (African American/African heritage), and co-administration of insulin as covariates of CL/F (Table 4).

In the final PK model, the exponential error model was used to characterize inter-individual variability for clearance. A combined proportional and additive error model was selected to characterize residual variability in the final PK model. Age and eGFR appeared to be closely related based in their collinearity and a similar magnitude of effect on CL/F. However, as eGFR exhibited a slightly greater drop in OFV, it was retained in the final model.

Table 4: Population PK parameters of final PK model

Parameters (Units)	Final Estimate	95% Bootstrap CI		Inter-individual Variability [a]
		Lower	Upper	
CL/F (mL/h) = $\theta_{CL} \times (WT/90.7)^{\theta_{CL\text{-}weight}} \times (eGFR/77.9)^{\theta_{CL\text{-}eGFR}} \times \theta_{CL\text{-}race} \times (\theta_{CL\text{-}insulin})^{INSN}$				34.9%
θ_{CL}	66.6	64.0	69.0	
$\theta_{CL\text{-}weight}$	0.932	0.0160	1.03	
$\theta_{CL\text{-}eGFR}$	0.219	0.117	0.315	
$\theta_{CL\text{-}race}$	0.778	0.723	0.832	
$\theta_{CL\text{-}insulin}$	1.22	1.01	1.49	
V/F (mL)	21200	18300	24000	Not estimated
Ka (h^{-1})	0.0314	0.0240	0.0414	Not estimated
AS1	0.670	0.639	0.697	Not estimated

Source: GSKGLPCMBPKC0613.sum (Attachment 2.2) and Attachment 2.5

[a] The magnitude of inter-individual variability was presented as CV%.

AS1 = assay shift factor; eGFR = estimated glomerular filtration rate in mL/min; WT = body weight in kg

Notes: Race effect equals $\theta_{CL\text{-}race}$ for African American/African heritage and otherwise equals 1.

INSN equals 1 for subjects receiving insulin as ongoing antidiabetic medication and 0 otherwise.

Final estimate and inter-individual variability were from NONMEM estimates.

Residual variability was modeled using both proportional and additive terms. The proportional error term had associated coefficient of variation of 24.9%; the additive error term had a standard deviation of 332 ng/mL.

Source: Population PK study report, pg 48

The sponsor observed changes in the concentration of albiglutide and attributed these to the ELISA readout method. The concentrations showed an upward shift in the period after July 1, 2010 as compared to those read before this date. The population PK included samples that were analyzed both pre and post-shift. The shift in albiglutide concentrations after the timeframe of July 2010 was not related to a single study or specific time-related factors within each study and could be accounted for in the PK modeling by inclusion of an assay shift parameter (AS1). This was described as a factor in the additive component of the residual variability. $\sigma = \varepsilon_1 * Cp + \varepsilon_2 * AS1$

The final PK model indicated that apparent clearance (CL/F) of albiglutide is a function of body weight (WT), eGFR, African American/African heritage, and co-administration of insulin (INSN). These covariates accounted for 7.5% of inter-individual variability of CL/F (i.e., decrease inter-individual variability from 42.4% to 34.9%.

Basic goodness of fit plots for the Sponsor's final model is shown in Figure 8.

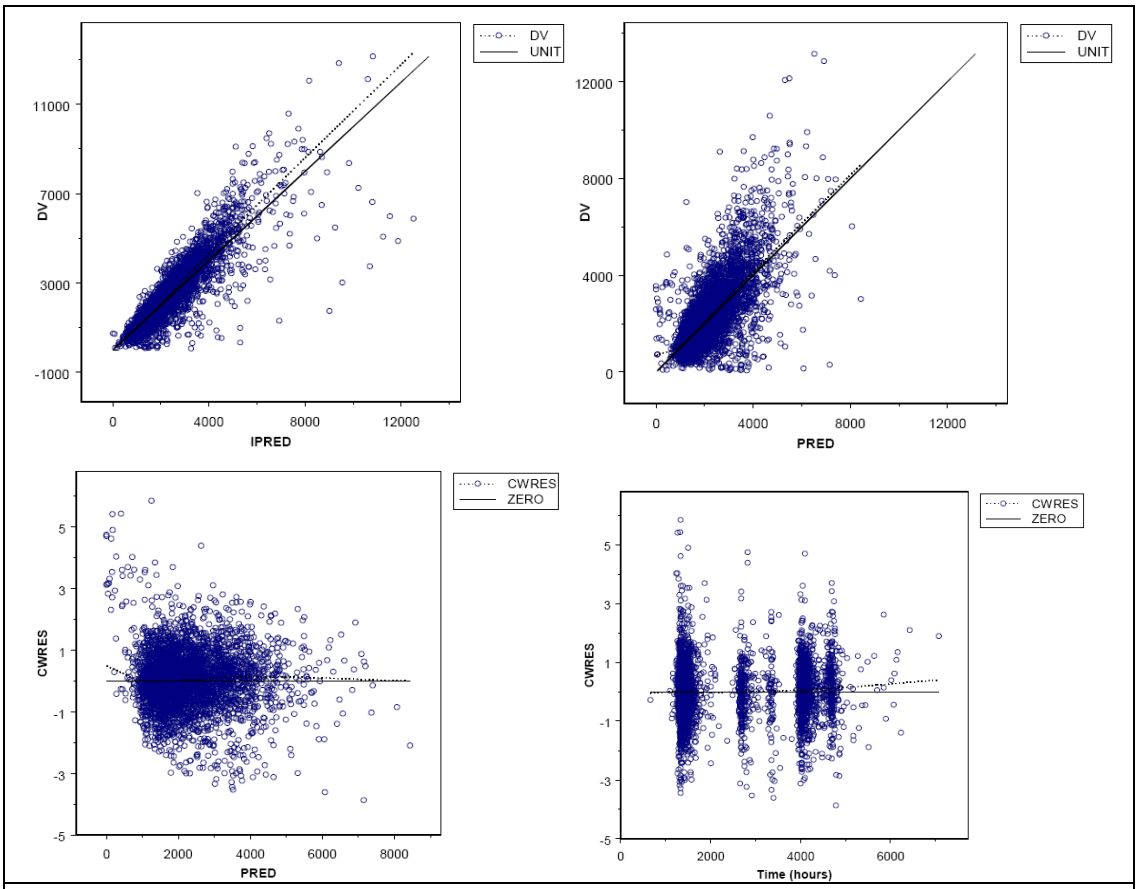


Figure 8: Basic goodness of fit plots for the Sponsor's final model
Source: Population PK Study Report, Page 89-90

The visual predictive check plots are presented using time after the first dosing. Median, 5th percentile, and 95th percentile plots of model-predicted outcomes vs. observed concentrations are presented as follows for each of the four studies used in population PK analysis and the combined plot of the four studies (Figure 9).

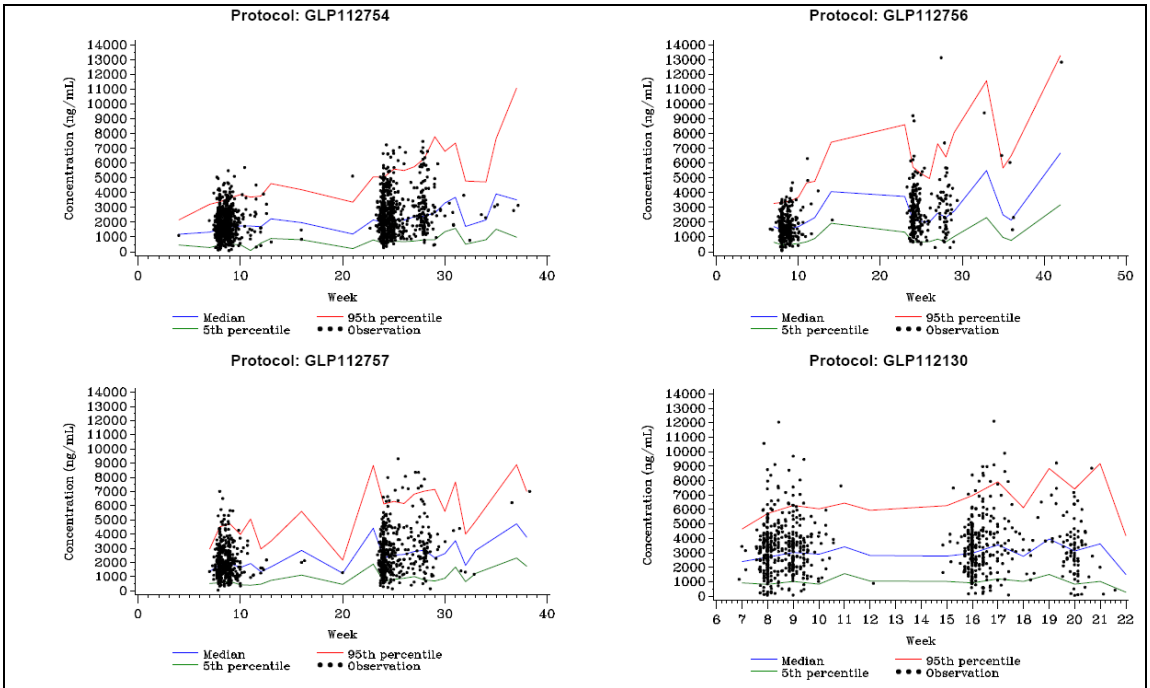


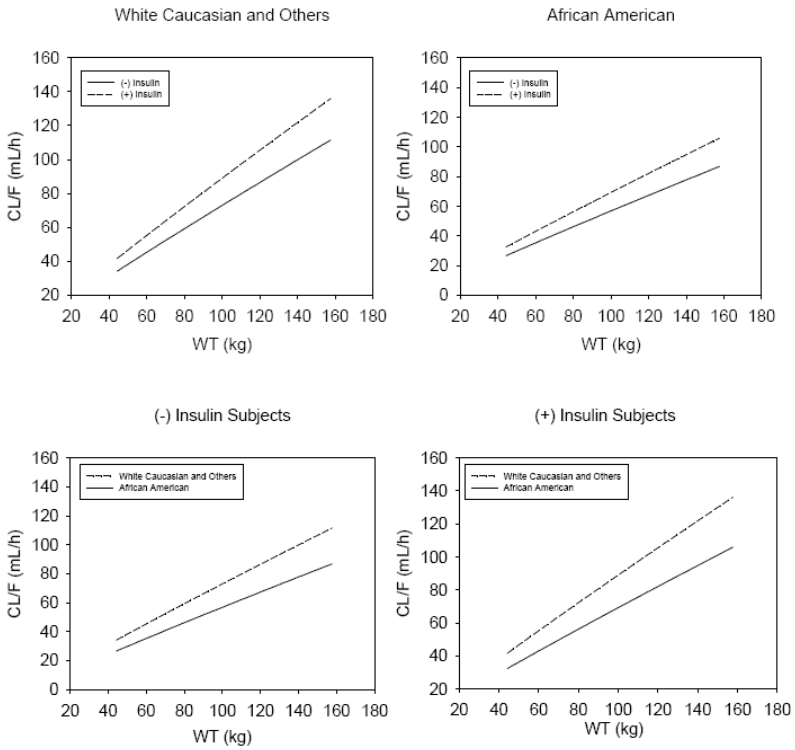
Figure 9: Model-predicted vs. observed albiglutide plasma concentration (Final PK model)
Source: Population PK Study Report, page 66

2.1.2.1 Albiglutide Covariate Effects

The relationship between CL/F and both covariates was:
CL/F (mL/h) = 66.6 × $(WT/90.7)^{0.932}$ × $(eGFR/77.9)^{0.219}$ × 0.778 (if African American/African heritage) × 1.22 (if receiving ongoing insulin medication)

Albiglutide CL/F was found to increase with increasing body weight and eGFR. The effect of changes in body weight on changes in CL/F is nearly proportional (i.e., 20% increase in body weight resulted in approximately 18.5% increase in CL/F). Over the ranges of body weight observed in this study, the mean estimate of CL/F in the lowest body weight (44.3 kg) could be as low as 0.51-fold of the average CL/F. The mean estimate of CL/F in the highest body weight (157.7 kg) could be as large as 1.67-fold of the average CL/F (Figure 10).

The effect of changes in eGFR on changes in CL/F is less than proportional (i.e., 20% increase in eGFR resulted in 4% increase in CL/F). Over the ranges of eGFR observed in this study, the mean estimate of CL/F in the lowest eGFR (15.6 mL/min) could be as low as 0.70-fold of the average CL/F. The mean estimate of CL/F in the highest eGFR (154 mL/min) could be as large as 1.16-fold of the average CL/F (Figure 11).



EGFR = estimated glomerular filtration rate; WT= body weight
Notes: Relationship displayed for a reference subjects with median EGFR
Insulin: (-) = no insulin, (+) = insulin taken as concomitant medication

Figure 10: Plots of Relationship between CL/F and Covariates from the Final PK Model
Source: Population PK Study Report, page 50

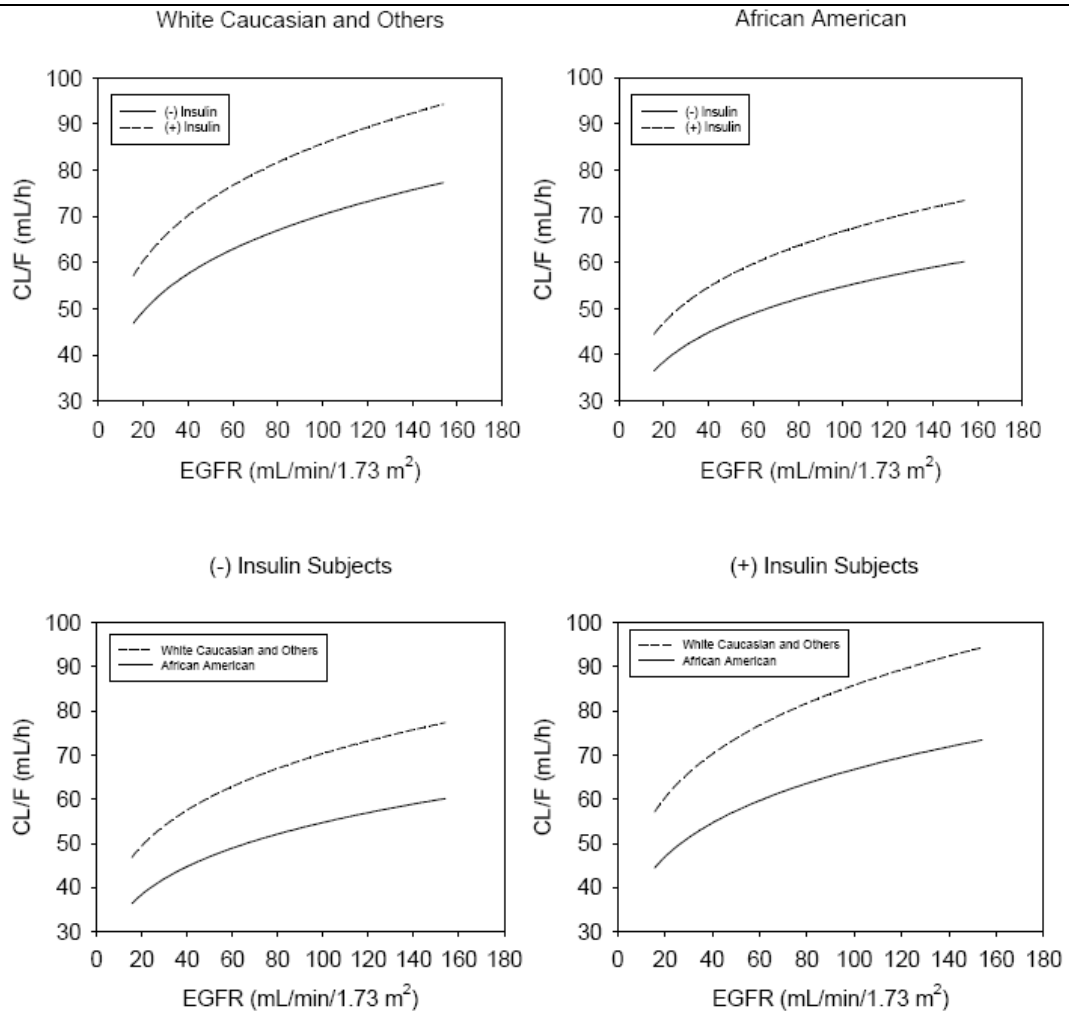


Figure 11: Plots of Relationship between CL/F and Covariates from the Final PK Model
Source: Population PK Study Report, page 51

Subjects who received insulin as an ongoing medication were associated with 22% higher CL/F. It should be noted that insulin was generally reserved in these studies as a rescue medication. There were only 22 subjects, all from study GLP114130, included in the PK NONMEM input file for whom insulin was indicated as a concomitant medication, rather than as a rescue medication only. The higher CL/F indicated by the model for insulin users was due to this small number of subjects. Therefore, it should be interpreted with caution and does not appear to be clinically meaningful.

African American/African heritage was associated with 22% lower CL/F. For a subject who is not of African American/African heritage weighing 90.7 kg with eGFR of 77.9

mL/min and not currently receiving insulin as an ongoing medication, the average CL/F value is 66.6 mL/h. A subject with the same characteristics who is of African American/African heritage has the average CL/F value of 51.8 mL/h (i.e., 22% lower CL/F than subjects of other races).

Immunogenicity: To evaluate the potential impact of anti-albiglutide antibodies on albiglutide PK and PD, correlations between antibody status/titers and PK/PD parameters were visually explored. Figure 12 presents albiglutide clearance in antibody positive and antibody negative subjects. There was no apparent relationship between clearance and antibody formation. Figure 13 displays albiglutide clearance versus antibody titer. No correlation between clearance and antibody titers was observed where albiglutide clearance is plotted versus antibody titer. Therefore, the antibody status or titer was not included in the covariate analysis.

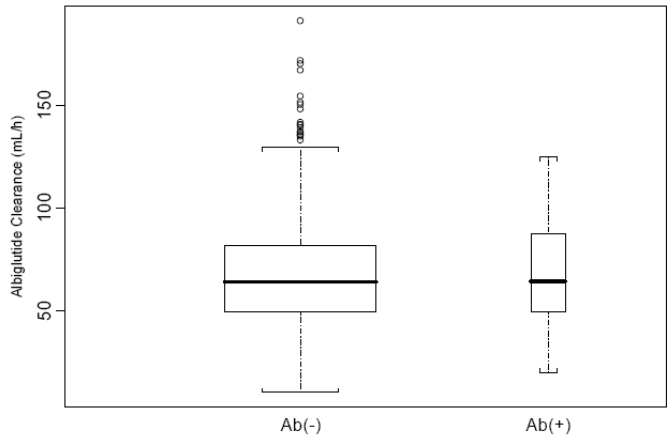


Figure 12: Albiglutide clearance in antibody positive and negative subjects. *Source: Population PK Study Report, page 46*

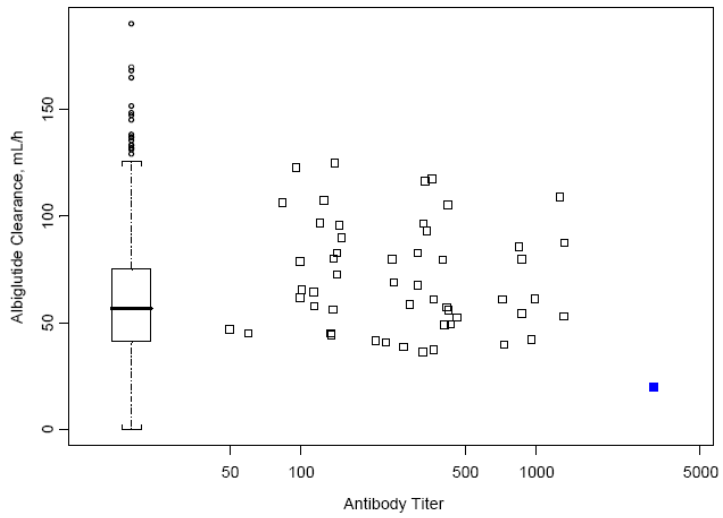


Figure 13: Albiglutide clearance versus Antibody Titer *Source: Population PK Study Report, page 46*

2.2 Sponsor's Conclusions

- A one-compartment PK model with first order absorption and elimination described the PK of albiglutide when administered subcutaneously in subjects with type 2 diabetes.
- (b) (4)
- The pre-shift concentrations were estimated to be approximately 33% lower than the post-shift concentrations.

Reviewer's comments on Sponsor's Population PK Analysis:

- *Sponsor's population PK analysis is generally adequate.*
- *While insulin use was identified as a covariate in sponsor's model, the data is limited to 22 subjects. In addition, the mechanism for this observed interaction is unclear and therefore this should be interpreted with caution.*
- *Assay shift: The sponsor observed an upward shift in the concentration of albiglutide and attributed the changes in the ELISA readout. There were magnitude differences in shift between certain trials (GLP112754; 18% increase & GLP108370; 61% increase). Sponsor attributed these to different manual pipetting speed between these two trials. Population PK samples from Studies GLP112754, GLP112756, and GLP112757 were collected at approximately Week 8 and Week 24 of each study. The exposure shift was clear among those subjects with samples that were analyzed both pre- and post-shift. For those subjects with Week 8 concentration samples analyzed before 1 July 2010 and Week 26 samples analyzed after 1 July 2010, the mean concentration changed from 1821 to 2793 ng/mL (approximately 1.5-fold increase). The subjects who had Week 8 and Week 24 samples analyzed post-shift had similar mean concentrations ranging from approximately 2700 to 3000 ng/mL. The variability (%CV) was consistent in samples analyzed pre- and post-shift. Thus, the results of post-shift are consistent. There was no indication of any non-random differences between the pre- and post-shift time periods. In addition, the single-dose bioequivalence study in treatment-naïve T2DM subjects administered in clinic (Study GLP114856) showed similar pharmacokinetics in terms of drug clearance as the post-shift Phase III program following 8 and 24 weeks dosing. Overall, the sponsor has justified that this shift occurs regardless of trials and is due to the ELISA readout. In the population PK, based on the samples that were analyzed both pre and post-shift the increase is consistent with those that were analyzed pos-shift only. The sponsor's approach to use the shift parameter in the population PK analysis seems reasonable.*

- *The covariates that were identified in the final model are likely not to be clinically significant as the magnitude of effect on systemic exposure of albiglutide is within 20-40%. Because albiglutide was found to be safe and tolerable at 30 mg once weekly subcutaneous regimen with the possibility for up-titration to 50 mg, the effects of covariates (body weight, eGFR, African American/African heritage, and insulin) on CL/F were not of a magnitude that would require dose individualization beyond the dosing regimen evaluated in the current Phase 3 studies. Sponsor's conclusion that no dose adjustment based on age, gender, body weight, and race is supported by the population PK analysis results and is acceptable. See reviewer's comments in section 1.3 and Figure 7.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RITESH JAIN
12/02/2013

JAYABHARATHI VAIDYANATHAN
12/02/2013

ANSHU MARATHE
12/02/2013

NITIN MEHROTRA
12/02/2013

LOKESH JAIN
12/03/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**125431**	**Brand Name**	**EPERZAN**
OCP Division (I, II, III, IV, V)	**DCP II**	**Generic Name**	**Albiglutide**
Medical Division	**DMEP**	**Drug Class**	**GLP-1 receptor agonist**
OCP Reviewer	**Ritesh Jain, Ph.D.**	**Indication(s)**	**Treatment of Type-2 Diabetes (T2DM)**
OCP Team Leader	**Lokesh Jain, Ph.D.**	**Dosage Form**	**Single use prefilled pen 30 mg and 50 mg albiglutide**
Pharmacometrics Reviewer		**Dosing Regimen**	**30 mg subcutaneously once weekly. Dose may be increased to 50 mg once weekly based on individual glycemic response**
Date of Submission	**01/14/2013**	**Route of Administration**	**subcutaneous**
Estimated Due Date of OCP Review	**11/01/2013**	**Sponsor**	**GlaxoSmithKline**
Medical Division Due Date	**11/08/2013**	**Priority Classification**	**S**
PDUFA Due Date	**01/14/2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	**X**			
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**2**		Study # GLP105229 Study # GLP107724: Effect of Injection site on PK of albiglutide
multiple dose:				
Patients-				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:	**X**	**1a**		Study # GLP107724: Effect of Injection site on PK of albiglutide
multiple dose:	**X**	**1**		Study # GLP106073
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	**X**	**4**		Study # GLP107032: OC DDI GLP108366: statin DDI GLP111680: digoxin DDI GLP111681: warfarin DDI
In-vitro:	**X**	**2**		Study # 7274-910, 05DMR078
Subpopulation studies -				
ethnicity:	**X**	**2a**		GLP107865: Japan Phase IIa; GLP110932: Japan Phase IIb;
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**		Study # GLP108370
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**5**		Study # GLP110125: Global Phase IIb; GLP107865: Japan Phase IIa; GLP110932: Japan Phase IIb; GLP114856: BE; GLP108372: Clamp Study;
Phase 3 clinical trial:	**X**	**4**		Study # GLP112754, GLP112756, GLP112757, and GLP114130
Population Analyses -				
Data rich:				
Data sparse:	**X**	**4a**		Study # GLP112754, GLP112756, GLP112757, and GLP114130
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		Study # GLP114856; Single dose BE comparing process 2 used in Phase2/3 trials to process 3 used for the TBM product.
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		Study # GLP107030: gastric emptying
Bio-waiver request based on BCS				
BCS class				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**21**		

[a] Studies were already counted elsewhere

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately	X			

	designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Sponsor is requesting a waiver for conducting pediatric studies in children 0 to <10 years of age and deferral in older children and adolescents ≥10 to <18 years of age
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____YES__

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
Please provide us with the data sets that were used for the Population PK and PK/PD Reports. All datasets used for model development and validation should be submitted as a SAS transport files (.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.*

*Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).*

In case you have submitted these data sets in the requested format, indicate its location.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Ritesh Jain	02/25/2013
Reviewing Clinical Pharmacologist	Date
Lokesh Jain	02/25/2013
Team Leader/Supervisor	Date

Filing Memo (Internal Memo)

(b) (4)

[redacted]

12 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RITESH JAIN
03/04/2013

LOKESH JAIN
03/04/2013