

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125431Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	BLA 351 (a)
Application Number(s)	BLA125431
Priority or Standard	Standard
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Division / Office	DMEP/ ODEII/OND
Reviewer Name(s)	Kaveeta P. Vasisht M.D., Pharm.D
Review Completion Date	October 17, 2013
Established Name	Albiglutide
(Proposed) Trade Name	Tanzeum
Therapeutic Class	GLP-1 Agonist
Applicant	GSK
Formulation(s)	Lyophilized powder contained within the single use prefilled pen providing 30 mg of albiglutide. Lyophilized powder contained within the single use prefilled pen providing 50 mg of albiglutide.
Dosing Regimen	30 mg or 50 mg every week
Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Intended Population(s)	Adults with Type 2 diabetes Mellitus

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## 1 Recommendations/Risk Benefit Assessment

Albiglutide is a GLP-1R agonist that acts on pancreatic beta cells to augment glucose-dependent insulin secretion. The sponsor is seeking an indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The applicant's proposed labeling indicates that albiglutide is not recommended as first-line therapy for patients inadequately controlled on diet and exercise (b) (4)

### 1.1 Recommendation on Regulatory Action

I recommend approval of albiglutide for the proposed indication, as there is substantial evidence of effectiveness from the eight pivotal Phase 3 trials.

I have summarized my rationale for this recommendation in section 1.2 below.

Since other disciplines and signatory authorities are still reviewing this application, the final language may differ from my recommendation.

### 1.2 Risk Benefit Assessment

The Phase III program included 8 clinical studies ranging from 8 months to 3 years designed to evaluate the efficacy and safety of two doses (30 and 50 mg) of once weekly subcutaneous (SC) injections of albiglutide in a broad spectrum of T2DM patients. Albiglutide was evaluated as monotherapy and as add-on to single, dual, and triple oral antidiabetic agents, and in combination with insulin glargine.

The proposed dose is 30 mg weekly as a SC injection increased to 50 mg weekly based on individual glycemic response. The clinical trials safety database for albiglutide includes a total of approximately 6258 subjects in Phase I-III trials with 5811 subjects having T2DM (3122 of these treated with 30 mg to 50 mg of albiglutide).

In the monotherapy trial (Study GLP112756) the least square mean (LSM) difference change in hemoglobin A1c (HbA1c) from baseline to the primary endpoint demonstrated superiority of albiglutide over placebo with both the 30 mg [-0.84% (95% CI: -1.11, -0.58)] and 50 mg [-1.04% (95% CI: -1.31, -0.77)] doses ( $p < 0.0001$ ). Albiglutide was also found to be non-inferior to pre-prandial insulin lispro and insulin glargine. A statistically significant difference from placebo in reduction of fasting plasma glucose (FPG) for both the 30 mg and 50 mg dose levels was also observed when compared to placebo. At the primary endpoint, the mean change in body weight ranged from +0.28

kg to -1.21 kg. Differences in weight change from placebo were not statistically significant.

Study GLP112753 compared albiglutide to placebo and active comparators; sitagliptin and glimepiride added on to background metformin. Albiglutide was statistically superior to placebo (-0.91%; 95% CI: -1.16, -0.65,  $p < 0.0001$ ) and non-inferior compared to sitagliptin (-0.35%; 95% CI -0.53, -0.17  $p < 0.0001$ ) and glimepiride (-0.27%; 95% CI -0.45, -0.09,  $p < 0.0001$ ). Superiority testing demonstrated that albiglutide was superior compared to both sitagliptin ( $p = 0.001$ ) and glimepiride ( $p = 0.0033$ ) at week 104.

The dedicated renal trial (Study GLP114130) demonstrated the effectiveness of albiglutide in subjects with T2DM with mild, moderate, or severe renal impairment with inadequate glycemic control. In comparison to sitagliptin, the magnitude of HbA1c reduction was significantly greater with albiglutide. The treatment difference (albiglutide - sitagliptin) was -0.32% (95% CI: -0.49, -0.15) in favor of albiglutide.

The efficacy assessment of albiglutide was reviewed against the safety profile data from the original BLA submission and the 120 day safety update. On-therapy deaths were balanced between albiglutide and all comparators. Overall the frequency of non-fatal serious adverse events (SAEs) was similar between subjects treated with albiglutide (10.6%) and all comparators (10.3%). The highest numeric imbalance in SAEs not in favor of albiglutide occurred in the system organ class of infections and infestations. Smaller numeric imbalances not in favor of albiglutide were also seen in the cardiovascular and gastrointestinal disorders organ classes. Non-fatal serious events of pneumonia, atrial fibrillation, and appendicitis occurred more frequently in the albiglutide group.

The application was reviewed for the following submission specific safety concerns which are described briefly below and in detail in Safety Section 7.3.5.

- **Thyroid Tumors:** No trend toward an increased risk of medullary thyroid cancer was identified in this review. However, numerous cases of anatomic thyroid abnormalities were not followed up by biopsy or imaging. Therefore determination of risk and causality is limited by lack of sufficient information.
- **Liver Enzyme Elevations:** A suspected case of drug induced hepatocellular injury was identified meeting criteria for biochemical Hy's law. Cases of hepatocellular injury manifesting in transaminase elevations have been observed with albiglutide treatment in the Phase 3 clinical program. Many cases were confounded with underlying cholestasis. Imbalances in gamma-glutamyl transpeptidase (GGT) elevations were observed to be not in favor of albiglutide when compared to all comparators and placebo treated subjects.

- Hypoglycemic Events: A higher incidence of hypoglycemic events occurred in the albiglutide group vs. placebo. Hypoglycemic events were higher when taking background insulin and/or sulfonylurea compared with subjects not taking background insulin and/or sulfonylurea.
- Gastrointestinal (GI) Events: Adverse events occurring in >5% of subjects treated with albiglutide with a higher incidence in the albiglutide group compared to placebo were in events of diarrhea and nausea.
- Immunogenicity: Approximately 5.5%, 116/2098 subjects treated with albiglutide tested positive for at least 1 post baseline anti-albiglutide antibody (9/116 had preexisting anti-albiglutide antibodies). The proportion of serious adverse events was generally balanced between antibody positive and negative subjects (12.9 vs. 11.4%, respectively). Injection site reaction (ISR) related discontinuations occurred for 5/45 albiglutide antibody positive subjects. All albiglutide-treated subjects who discontinued treatment for a potential systemic allergic reaction were anti-albiglutide antibody negative.
- Injection Site Reactions: A higher proportion of subjects in the albiglutide treatment group experienced an ISR compared with placebo treated subjects and all comparators. More subjects treated with albiglutide withdrew from treatment for injection site reactions (2.1% vs. 0.4%) and injection site rash compared to placebo.
- Systemic Allergic Reactions (SARs): Overall SARs in the albiglutide vs. placebo comparison group were balanced (1.8 vs. 1.9%). Subjects receiving albiglutide experienced systemic allergic reaction events of rash, angioedema and possible anaphylaxis.
- Pancreatic Events: A higher incidence of acute pancreatitis occurred in albiglutide treated subjects vs. placebo and all comparators. There was 1 fatal case of post endoscopic retrograde cholangiopancreatography (ERCP) necrotizing pancreatitis and 1 case of metastatic pancreatic cancer in the albiglutide treatment arm.
- Diabetic Retinopathy: Subjects receiving albiglutide had a higher frequency of diabetic retinopathy events compared to placebo (3.6 % vs. 1.7%, respectively). However funduscopy was not conducted in a rigorous and consistent manner in the clinical program.
- Cardiovascular Events: A cardiovascular meta-analysis was conducted for the Major Adverse Cardiovascular Events Plus (MACE-plus). This was a composite endpoint consisting of cardiovascular death, myocardial infarction, stroke, and

hospitalization for unstable angina. Based on the primary analysis model, the hazard ratio estimate of albiglutide versus comparator is 0.93 with corresponding 97.55% CI (0.55, 1.58). This meets the FDA requirements for filing and approval.

### Renal impairment

Study GLP114130 evaluated the efficacy of albiglutide in subjects with T2DM who had mild, moderate, and severe renal impairment determined by using the modification of diet in renal disease formula (See Section 5.3.1.1). Mild renal impairment was defined as an eGFR of  $\geq 60$  and  $\leq 89$  mL/min, moderate renal impairment was defined as an eGFR of  $\geq 30$  and  $\leq 59$  mL/min, and severe renal impairment was defined as an eGFR of  $\geq 15$  and  $\leq 29$  mL/min.

The model adjusted change from baseline at week 26 was greater in the albiglutide group for all 3 categorizes of renal impairment when compared to sitagliptin. The treatment difference at week 26 (albiglutide - sitagliptin) was  $-0.13$  (95% CI:  $-0.37, 0.11$ ),  $-0.53$  (95% CI:  $-0.80, -0.26$ ), and  $-0.47$  (95% CI:  $-1.12, 0.18$ ) for subjects with mild, moderate and severe renal impairment, respectively.

While the efficacy of albiglutide was demonstrated in severe renal impairment, the overall sample size in the dedicated renal study was small in the severe impairment category (N=19 for the albiglutide group and N=17 for the sitagliptin group). The percentage of subjects in the albiglutide arm with on-therapy hypoglycemic events was higher in subjects with severe renal impairment (26.3%, n=5) than in subjects with mild (10.9%, n=14) or moderate (9.8%, n=10) renal impairment. In the albiglutide group, on-therapy gastrointestinal (GI) adverse events occurred with a higher incidence and higher event rate in subjects with severe renal impairment compared with mild or moderate renal impairment (mild n=35, moderate n=35, severe n=9). Due to the small sample size in the severe renal impairment category conclusions are limited. However because GI events may worsen renal function, caution should be utilized when initiating or escalating doses of albiglutide in patients with severe renal impairment (creatinine clearance  $< 30$  ml/min). Albiglutide has not been studied in subjects with end stage renal disease (eGFR  $< 15$  ml/min) and therefore the safety and efficacy in this population has not been established. I am not recommending use in subjects with end stage renal disease (eGFR  $< 15$  ml/min)

In a population pharmacokinetic analysis in subjects 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.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The applicant submitted the following pharmacovigilance plan as described in Table 1

**Table 1: Sponsor Proposed Pharmacovigilance Plan**

Safety Concern	Pharmacovigilance (PV)	Risk Minimization (RM)
Important Identified Risks		
Acute Pancreatitis	<p>Continued utilization of the IDMC through end of ongoing Phase III studies</p> <p>Continued adjudication of possible pancreatitis by a Pancreatitis Adjudication Committee, including reports received from ongoing or future clinical trials and from the postmarketing setting</p> <p>Observational studies utilizing insurance claims data and electronic medical records to characterize risk, first for currently marketed GLP-1R agonists to provide a baseline assessment and post-approval as experience accumulates to utilize observational studies to evaluate the risk of pancreatitis with albiglutide compared to other antidiabetic agents.</p> <p>Targeted follow-up questionnaire specific for pancreatitis reported in association with albiglutide will be developed for the postmarketing experience</p> <p>Periodic cumulative reviews of individual case reports of pancreatitis from all sources (e.g. at time of periodic safety update report)</p>	<p>Product Labeling: Warnings regarding the event and precautionary guidance for patient selection and action to take if event occurs;            description of the clinical trials experiences</p> <p>Medication Guide</p> <p>REMS Communication Plan</p>

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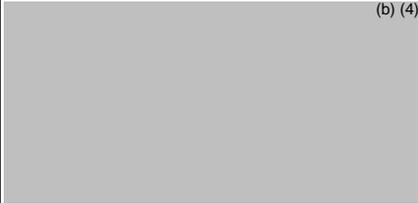
<p>Gastrointestinal events (e.g., nausea, vomiting, diarrhea)</p>	<p>Continued utilization of the IDMC through end of ongoing Phase III studies</p> <p>Re-assess safety profile as additional safety data emerge from ongoing and future clinical studies</p> <p>Routine postmarketing pharmacovigilance</p> <p>Close monitoring of serious GI related events or serious sequelae of GI events with expert case review on an as needed basis</p>	<p>Precautionary guidance in product labeling for use in patients with severe gastroparesis</p> <p>Describe clinical trials experience and adverse reactions in product labeling</p>
<p><b>Safety Concern</b></p>	<p><b>Pharmacovigilance (PV)</b></p>	<p><b>Risk Minimization (RM)</b></p>
<p>Hypoglycemia</p>	<p>Continued utilization of the IDMC through end of ongoing Phase III studies</p> <p>Re-assess safety profile as additional safety data emerge from ongoing and future clinical studies</p> <p>Routine postmarketing pharmacovigilance</p>	<p>Product labeling to include precautionary guidance regarding an increased risk of hypoglycemia when albiglutide is used in combination with insulin or insulin secretagogues and a possible need for dose reduction of these agents</p> <p>Guidance in dosage and administration, when starting albiglutide it may be necessary to reduce the dose of concomitantly administered insulin or insulin secretagogues to reduce the risk of hypoglycemia</p>

Injection Site Reactions	<p>Continued utilization of the IDMC through end of ongoing Phase III studies</p> <p>Re-assess safety profile as additional safety data emerge from ongoing and future clinical studies</p> <p>Routine post marketing pharmacovigilance</p>	Describe clinical trials experience and adverse reactions in product labeling
Pneumonia	<p>Continued utilization of the IDMC through end of ongoing Phase III studies</p> <p>Re-assess safety profile as additional safety data emerge from ongoing and future clinical studies</p> <p>Routine post marketing pharmacovigilance</p>	Describe clinical trials experience and adverse reactions in product labeling
<b>Safety Concern</b>	<b>Pharmacovigilance (PV)</b>	<b>Risk Minimization (RM)</b>
Atrial fibrillation/Atrial flutter	<p>Continued utilization of the IDMC through end of ongoing Phase III studies</p> <p>Re-assess safety profile as additional safety data emerge from ongoing and future clinical studies</p> <p>Routine post marketing pharmacovigilance</p>	Describe relevant clinical trials experience in product labeling
<b>Important Potential Risks</b>		

<p>Medullary thyroid cancer</p>	<p>If feasibility of the assay systems is established, nonclinical studies will be conducted to (1) determine potential of albiglutide to produce thyroid C-cell proliferation in mice relative to a well characterized, commercially available GLP-1R agonist, and (2) determine GLP-1R expression in human thyroid C-cells compared to rodent.</p> <p>Continued utilization of the IDMC through end of ongoing Phase III studies</p> <p>Re-assess safety profile as additional safety data (cases and serum calcitonin) emerge from ongoing and future clinical studies</p> <p>Targeted follow-up questionnaire specific for thyroid cancer reported in association with albiglutide in the post marketing experience will be developed</p> <p>Expert case review of MTC reports as needed</p> <p>Participation in Multi-Sponsor - American Thyroid Association MTC Registry (anticipated)</p> <p>Periodic cumulative reviews of individual case reports of MTC from all sources (e.g. at time of periodic safety update report)</p>	<p>Consistent with currently marketed GLP-1R agonists for treatment of T2DM, the proposed product labeling to provide a boxed warning regarding the potential risk of MTC</p> <p>Labeling includes a contraindication for use in patients with personal or family history of MTC or personal history of MEN2</p> <p>Specific warnings regarding the event and precautionary guidance for patient selection and action to take if event occurs</p> <p>Medication Guide</p> <p>REMS Communication Plan</p>
<p><b>Safety Concern</b></p>	<p><b>Pharmacovigilance (PV)</b></p>	<p><b>Risk Minimization (RM)</b></p>

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Cardiovascular safety of antidiabetic therapy	<p>Continued utilization of the IDMC through end of ongoing Phase III studies</p> <p>Continued adjudication of possible MACE+ by CEC through completion of 5 ongoing Phase III studies and in the planned Japan Phase III studies</p> <p>Confirm results for 2 year CV meta-analysis by incorporating 3 year data from the completed 5 core Phase III clinical studies</p> <p>To fulfill the FDA "Guidance for Industry on evaluating cardiovascular risk in new antidiabetic therapies to treat Type 2 diabetes" additional evaluation of cardiovascular safety (MACE+ endpoints) will be required; options for additional investigations are under discussion and will be agreed with the agency prior to finalization of plan.</p>	
Immunogenicity (e.g., clinical sequelae of antidrug antibodies, severe hypersensitivity reactions, other immune related events)	<p>Continued utilization of the IDMC through end of ongoing Phase III studies</p> <p>Re-assess safety profile as additional safety data emerge from ongoing and future clinical studies</p> <p>Routine post marketing pharmacovigilance</p>	Describe relevant clinical trials experience in product labeling
Hepatotoxicity	<p>Continued utilization of the IDMC through end of ongoing Phase III studies</p> <p>Re-assess safety profile as additional safety data emerge from ongoing and future clinical studies</p> <p>Routine post marketing pharmacovigilance</p>	Maintain global Phase III eligibility criteria and liver safety monitoring and follow up algorithm for Japan Phase III program
<b>Safety Concern</b>	<b>Pharmacovigilance (PV)</b>	<b>Risk Minimization (RM)</b>

Missing or Limited Information		
Use in pregnancy and Lactation	<p>Analysis of additional safety data that may arise from any ongoing or future clinical studies</p> <p>Routine post marketing pharmacovigilance</p>	Guidance regarding use in pregnancy and lactation in product labeling
Use in pediatric population	<p>Nonclinical studies planned to assess potential risk of accelerated sexual maturation</p> <p>Pediatric development plan submitted with this BLA [m1.9.4 Proposed Pediatric Study Request] to include ages <math>\geq 10</math> years to <math>&lt; 18</math> years, propose studies anticipated to begin no sooner than 3 years post launch of approved product</p> <p>Routine post marketing pharmacovigilance</p>	Product labeling to acknowledge absence of data to support use in pediatric population
Use in patients with hepatic impairment	Routine post marketing pharmacovigilance	<p>Product labeling to describe limitation of experience</p> <p>(b) (4)</p> 

Source: BLA125431 Module 1.16, Section 5.3, Page 31.

Additional recommendations are detailed in Section 1.4 and throughout the safety review (Section 7).

#### 1.4 Recommendations for Postmarket Requirements and Commitments

The applicant will be required to conduct a dedicated study to assess for increased cardiovascular risk in high risk patients per the FDA *Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. The primary objective of this trial will be to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with albiglutide to that observed in the control group is less than 1.3.

Adverse events of special interest that should be monitored in the dedicated cardiovascular outcomes trial (CVOT) include; pancreatitis, thyroid cancer, hepatotoxicity, systemic allergic reactions, hypoglycemia, gastrointestinal events, immunogenicity, injection site reaction, diabetic retinopathy, pneumonia, atrial fibrillation/flutter, appendicitis, GGT elevations and gastrointestinal events in association with renal impairment. A study evaluating gallbladder ejection fractions in albiglutide treated subjects is recommended to further characterize any relationship between albiglutide and elevated GGT levels.

In addition to the pharmacovigilance plan delineated in Table 1 (Section 1.3), post marketing cases of malignancy should be thoroughly followed through enhanced pharmacovigilance. The applicant should also specifically monitor cases of pancreatic cancer, hematologic malignancies (acute myeloid leukemia and lymphoma) which demonstrated a small imbalance not in favor of albiglutide.

Cumulative death data demonstrated that the neoplasms SOC had the highest proportion of deaths for both treatment arms (0.3% albiglutide vs. 0.4% all comparators). Most neoplasm events were single events and did not demonstrate a consistent pattern. In the albiglutide arm 2 subjects had fatal events related to lung cancer. There was a higher number of lung cancer related fatalities in all comparators when combining events of metastatic, malignant and non-small cell lung cancer. Review of non-fatal serious adverse events revealed 3 events related to lung cancer in the albiglutide group and 2 in all comparators. Due to the overall higher number of lung cancer related events compared to other malignancies lung cancer should monitor through post marketing pharmacovigilance.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Albiglutide is a GLP-1R agonist that acts on pancreatic beta cells to augment glucose-dependent insulin secretion.

The to-be-marketed drug substance (also known as GSK716155) is a recombinant human glucagon-like peptide 1 (GLP-1) human albumin fusion protein that consists of two copies of a 30-amino acid sequence of modified human GLP-1 (fragment 7-36) genetically fused in series to human albumin (See Figure 1). The first modified GLP-1 copy is fused at its <sup>(b) (4)</sup> of the second copy. This peptide in turn is genetically fused at its <sup>(b) (4)</sup> of human albumin.

#### Figure 1: Albiglutide Structure Formulation



The GLP-1 sequence has been modified with a glycine substituted for the naturally-occurring alanine at position 8 to confer resistance to DPP-IV mediated proteolysis.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

Type 2 diabetes is treated with a combination of proper diet, exercise, and the following classes of drugs given as monotherapy or in combination:

- Insulin and insulin analogues
- Sulfonylureas (SU)
- Biguanides
- Meglitinides
- Thiazolidinediones (TZDs)
- Inhibitors of alpha-glucosidase
- Analogues of Glucagon-like Peptide 1 (GLP-1)
- Synthetic analogues of human amylin
- Inhibitors of the enzyme dipeptidyl peptidase 4 (DPP-IV inhibitors)
- Bile acid sequestrants
- Dopamine agonists
- Amylin Analogues

### 2.3 Availability of Proposed Active Ingredient in the United States

Albiglutide is a new molecular entity and is currently not approved in the United States.

### 2.4 Important Safety Issues with Consideration to Related Drugs

Labeled safety concerns with other GLP-1 agonists include:

1. Acute pancreatitis
2. Gastrointestinal side effects
3. Hypoglycemia in combination with sulfonylurea or insulin use
4. Hypersensitivity reactions
5. Thyroid C cell tumors
6. Renal impairment secondary to gastrointestinal adverse events

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

**Table 2: Presubmission Regulatory Activity**

Date/Serial No. (SN)	Type of Interaction	Description
12Aug2008	GSK/FDA EOP2 <sup>1</sup> Meeting	EOP2 Meeting to discuss Phase III clinical program to support BLA filing
17Nov2008	Correspondence	Follow-up to EOP2 meeting and revised clinical development plan
30Jun2009	FDA Correspondence	FDA comments on 5 Phase III protocols, draft definitions for CV outcome trials
27Aug2009	FDA Advice	Class labeling for pancreatitis and thyroid C-cell tumors – request for modification of clinical trials
06Nov2009 SN0212	Gen Correspondence	CV Analysis Plan
01Jul2010	FDA Correspondence	Advice re CV analysis plan: Attached updated FDA draft definitions for unstable angina and hospitalization for CHF
21Sep2010	GSK/FDA Type B CMC Mtg	Discussion of Process 3 change in site, scale and process, introduction of Process 3 material into Phase III studies;
17Feb2011	FDA Response	Re need for QT study
30Mar2011	Response to FDA	Revised CV Analysis plan
26May2011	GSK/FDA Type C CMC Meeting	Request for clarification of comparability plans and requirements for BLA
28Jul2011	FDA Correspondence	Albiglutide as biologic therefore BLA

07Mar2012 SN0397	PPSR	Request for waiver for <10 years with request for deferral in 10 to 18 years for described study
12Mar2012	FDA Letter	FDA unable to issue Pediatric Waiver until albiglutide approved for adults.
13Mar2012 SN0398	Request for FDA Feedback	Comparability proposal
18Apr2012	FDA Letter	Type C meeting granted as written response within 60 days of submission of briefing information
08May2012 SN0404	Type C Clinical and Nonclinical Briefing Package	3 nonclinical and 20 clinical/other questions
22May2012 SN0406	Response to FDA	Response to 15May2012 email re pancreatitis monitoring
19Jun2012	FDA Advice Letter	GLP-1R agonists and concerns regarding sexual maturation
06Jul2012	FDA Letter	Responses to Type C Briefing Packages SN0404 and SN0405
10Oct2012	GSK/FDA pre-BLA Meeting	Discussion of selected FDA responses to questions re FcRn, RP-HPLC integration practices, CV meta-analysis results, inclusion of GLP114856 Part 2 CSR in BLA, pancreatitis presentation, and blinding.
15Nov2012 SN0422	Response to FDA	Response to pre-BLA comments on immunogenicity (corrected)

\* Cut-off date of 01 Dec 2012. 1=EOP2 (End of Phase 2).

## 2.6 Other Relevant Background Information

During the clinical development of albiglutide there were three manufacturing processes used to produce albiglutide drug substance: Process 1, Process 2 (Phase III drug substance) and Process 3 (commercial formulation). Clinical comparability for Process 2 albiglutide used in Phase III studies compared to the Process 3 commercial product is based on bioequivalence Study GLP114856 as well as blinded switching of subjects from Process 2 to Process 3 product in Phase III studies GLP112754 and GLP112756. In these two pivotal trials, patients were randomized to albiglutide Process 2 materials until the primary endpoint and then switched to the Process 3 to be marketed product in September 2011 during the safety extension phases.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The applicant utilized a masking procedure to ensure the integrity of the studies since 5 of the studies were ongoing at the time of BLA submission. Scrambled site ID/subject numbers were used to mask the true site ID/subject numbers. All results were reported

using the scrambled site ID/subject number (masked data). The applicant states that the internal development team was divided into two groups: the submission team, (which had full access to all subject level masked data), and the site-facing operations team, (which did not have access to the masked data and remained blinded). An independent unblinded team generated “masked” site/subject IDs for the study. Masking of data was undertaken for open-label and for blinded studies.

The quality of the submitted phase III clinical data was reasonably sufficient. Deficiencies related to safety assessments were:

- Lack of relevant clinical details in the narratives.
- Concerns regarding the stability of biomarker samples used for baseline assessment for calcitonin, amylase and lipase.

### 3.2 Compliance with Good Clinical Practices

The sponsor states that all studies were conducted in accordance with ICH guidelines on GCP, and all applicable subject privacy requirements and ethical principles were in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted.

#### Sites Closed by Sponsor

At the time of the BLA submission, the applicant stated that four sites in the US (Dr. Larsen sites 3636 and 1277; Dr. Wolfson sites 3525 and 1166) and one site in Mexico (Dr Sanchez site 5464) were closed, reported to the FDA and discontinued from the trial because of repeated noncompliance with GCP/ICH guidelines. These three investigators randomized a total of 64 subjects.

***Reviewer Comment: Data from these subjects were included in the safety and efficacy analyses. The applicant states that in each of the Phase III studies, a sensitivity analysis was performed at the primary efficacy endpoint (Intent-to-Treat population) to exclude subjects from the sites closed by GSK. Results of the sensitivity analyses were noted to be similar to the primary endpoint analyses. After the BLA submission 3 additional sites were terminated by GSK.***

Seven sites involved in the pivotal efficacy and safety studies were inspected by the Division of Scientific Investigations. These sites were selected due to high enrollment, multiple study participation and high efficacy.

- #1: Site 1200/3669, Richard Stewart, Atlanta, GA
- #2: Site 460/8001, Paramesh Shamanna, Bangalore, India
- #3: Site 1325/3784, John Gabriel, North Richland Hills, Texas

- #4: Site 1083/3442, Jean-Louis Selam, Tusin, CA
- #5: Site 1001/3460, Opada Alzohaili, Dearborn, MI
- #6: Site 1294/3653, Gary Ruoff, Kalamazoo, MI
- #7: Site 1242/3601, Simon Babazadeh, Santa Ana, CA

Site 1001/3460 (Investigator: Opada Alzohaili) received an OAI inspection classification for poor study conduct (See Dr. Kleppinger's review).

#### Duplicate Subjects

Across the P3-ISP in 5 of the 8 studies (GLP112753, GLP112754, GLP112756, GLP112757 and GLP114130), there were 16 unique subjects that enrolled themselves in the same study at multiple sites or in some instances in a different study at multiple sites. Follow up information obtained from the applicant clarified that at the time of discovery, all subjects were immediately withdrawn from treatment and then assigned to one study site. Those subjects who enrolled in multiple studies were assigned to a single site in one study for annual follow-up. In total, this represented 40 unique instances of "duplicate subjects" across the program:

- GLP112753: 20 unique instances
- GLP112754: 13 unique instances
- GLP112756: 4 unique instances
- GLP112757: 1 unique instance
- GLP114130: 2 unique instances

The applicant states that due to the relatively small number of overall duplicate subjects in the Phase III program, these duplicate subjects were included in the primary integrated analysis for each of the treatment group(s) in which they were enrolled. All subjects who received study medication were included in the integrated safety analyses. Of note, Study GLP114130 was not included in the integrated analysis of safety and efficacy and therefore the 2 instances of duplicate enrolment identified in this study did not impact the final integrated analyses. A sensitivity analysis specifically excluding these data was not performed, as omitting these 38 unique incidences (0.9% of the total BLA Integrated Safety Population) would have minimally impacted the results.

***Reviewer Comment: The following information request was sent to the applicant and was pending at the time of this review. Any changes in recommendations resulting from review of the applicant's response will be added as an addendum to this review.***

***We are requesting that you conduct the following efficacy analyses in support of your application. In each of the 8 pivotal Phase III studies, conduct a sensitivity analysis for the primary efficacy endpoint of HbA1c***

***(Intent-to-Treat population) excluding subjects from the sites closed by GSK, duplicate subjects in the clinical program and any data from Site 1001/3460 (principal investigator Opada Alzohaili). In addition, conduct sensitivity analyses for fasting plasma glucose, body weight and percent of subjects obtaining an HbA1c <7% at the time of the primary endpoint. Specify the number of subjects removed in each sensitivity analysis compared to the primary analysis.***

#### Serum Sample Stability Issue (Calcitonin, Amylase, Lipase)

During an OSI inspection the agency became aware that baseline values for amylase, lipase and calcitonin may have been drawn from stored biomarker samples that were past the serum stability period. The applicant was asked to clarify the stability of biomarker samples used for baseline assessment and provide information (total number of subjects) regarding labs drawn from a sample that was past the validated serum stability period.

*The applicant's responses are described below.*

#### Calcitonin Measurement

The sponsor requested (b) (4) to conduct retrospective assays on stored exploratory biomarker samples collected at baseline (September 2009). Validated storage stability for the calcitonin assay was up to 28 days (per (b) (4) specifications). The applicant notes that GSK was advised that calcitonin had a far greater stability in serum under the storage conditions in place therefore, GSK took a decision in September 2009 for research purposes to request analysis of the older stored biomarker samples for calcitonin (some of which had exceeded the stability limit per the (b) (4) assay validation of up to 28 days storage).

Of note, the retrospective testing of biomarker samples to obtain a baseline value for subjects enrolled prior to Protocol Amendment 01 was completed by (b) (4) in December 2009. Long-term storage stability studies were subsequently initiated by (b) (4) in November 2009 and January 2010 to evaluate the longer-term frozen (-70°C and -20°C, respectively) stability for serum calcitonin assays. These stability studies were completed in June 2010 and the results validated the use of stored biomarker samples for use in the calcitonin assay under the storage conditions of the protocols for up to 6 months (the stability validation study did not go beyond 6 months).

The applicant states that in the worst case, the biomarker samples for 428 of 2554 subjects (16.76%) with baseline samples were beyond the longer term stability of 6 months. For each of the five, 3-year studies, a sensitivity analysis was conducted to analyze the change from baseline in calcitonin by visit,

excluding subjects with a baseline calcitonin value obtained from a stored biomarker sample. The applicant notes that the results of the sensitivity analyses were similar when including and excluding subjects with calcitonin values obtained from a baseline biomarker sample.

### Amylase/Lipase Measurement

The sponsor requested (b) (4) to conduct retrospective assays on stored exploratory biomarker samples collected at baseline (September 2009). The validated storage stability for the amylase and lipase assays was up to 6 months (per (b) (4) specifications). Of note, the retrospective testing of biomarker samples to obtain a baseline value for subjects enrolled prior to Protocol Amendment 01 was completed by (b) (4) in December 2009. In February 2011, (b) (4) initiated studies to evaluate the long-term frozen stability for serum amylase and lipase samples stored at -20°C and -70°C. These rolling studies were completed in March 2013 and the results validated the assays under the storage conditions for up to 24 months. There were no amylase or lipase values tested > 24 months.

### Pen Failures

Refer to review by Dr. Lana Shiu from the Office of Device Evaluation regarding the root cause and corrective actions for pen related events.

Reports of pen injector customer complaints revealed a total of 859 complaints and 330 user errors. The applicant was asked to summarize the potential clinical impact of pen related issues on efficacy and safety.

In total, 76 partial doses were recorded across the program and 56 product complaints were recorded. Across the clinical program no events of partial dose received were seen in consecutive weeks. Where product complaints were registered, 39/56 (70%) resulted in pen replacement and only one event of hyperglycemia was reported in subjects where a partial dose was received. The sponsor's clinical impact statement notes that pen failures were not likely to have impacted interpretation of albiglutide clinical trial results.

### **3.3 Financial Disclosures**

The applicant submitted a signed form FDA 3454 dated November, 27th, 2012, along with a list of investigators involved in the 8 pivotal Phase 3 studies (GLP108486, GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP114179, and GLP114130) and Phase 2 study GLP114864. On this form box 1 is checked certifying that the sponsor had not entered into any financial arrangement with the listed clinical

investigators that could affect the outcome of the study as defined by 21 CFR 54.2(a), and further certifying that none of the investigators disclosed having a proprietary interest in the study drug product or a significant equity in the sponsor as defined in 21 CFR 54.2(b).

GSK was unable to obtain financial information at the end of the study for ten (10) Principal Investigators/Former Principal Investigators as described in Table 3.

**Table 3: Investigators Lacking Financial Information**

	<b>Principal/ Former Principal Investigator</b>	<b>Study</b>	<b>Actual Subjects seen during PI tenure</b>	<b>Reason</b>
1	Janet McGill	GLP108486		Failed to submit
2	Cynthia Sadler	GLP108486 GLP112753 GLP112754 GLP112755 GLP112756 GLP112757	5/779 1/310 4/309 2/685	Refused to sign a financial disclosure
3	Gopalkrishna Gollapudi	GLP112753		Deceased
4	Armando Perez	GLP112753		Refused to sign a financial disclosure
5	Norman Lunde	GLP112754 GLP112755 GLP112757 GLP114130	3/779 0/310 1/685 1/507	No longer affiliated with the site and refused to sign a financial disclosure
6	Bret Wittmer	GLP112754	1/779	Deceased
7	Sean Castellucci	GLP112757	0/685	Failed to submit a financial disclosure
8	Jose Nunez	GLP114130	4/507	No longer affiliated with the site and is no longer practicing
9	Manuel Suarez	GLP114130	7/507	Failed to submit a financial disclosure
10	Donald Huffman	GLP114856	2/225	Failed to submit a financial disclosure

Source: BLA 125431 -Generated from the Financial Disclosure Information in Section 1.3.4

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

See relevant review by Dr. Joao Pedras-Vasconcelos.

During the clinical development of albiglutide, three manufacturing processes were used to produce the drug substance (Process 1, Process 2, and Process 3). (b) (4)

 The commercial product remains a DCC in a pen injector.

***Reviewer Comment: Dr. Pedras-Vasconcelos concluded that the quality of the Process 3 product was acceptable.***

### 4.2 Clinical Microbiology

Dr. Bo Chi and Dr. Lakshmi Narasimhan's clinical microbiology reviews were pending at the time of this clinical review.

### 4.3 Preclinical Pharmacology/Toxicology

See review by Dr. Ronald Wange.

Dr. Wange recommends approval but notes that albiglutide was highly immunogenic in animals. In his review, Dr. Wange states that in mice the antidrug antibody (ADA) response caused diminished exposure to albiglutide and was associated with type 3 hypersensitivity reactions (immune complex deposition) in a subset of animals. He notes that the sponsor will conduct a juvenile toxicity study in a rodent model prior to initiation of pediatric trials with albiglutide.

### 4.4 Clinical Pharmacology

Dr. Ritesh Jain's review was pending at the time of this clinical review. Internal discussions with the clinical pharmacology team have identified no significant concerns to date.

#### 4.4.1 Mechanism of Action

Albiglutide is an agonist of the GLP-1 receptor (GLP-1R) and augments glucose-dependent insulin secretion and slows gastric emptying.

#### 4.4.2 Pharmacodynamics

Please refer to Dr. Ritesh Jain's Clinical Pharmacology Review for details.

Albiglutide lowered fasting glucose and reduced postprandial glucose excursions. After receiving 32 mg of albiglutide on Days 1 and 8, there was an 18.5% reduction in postprandial glucose (following a standardized breakfast meal on Day 9). The difference was statistically significant and occurred at a clinically relevant dose used in the Phase III studies (30 mg).

#### 4.4.3 Pharmacokinetics

The primary route of absorption following subcutaneous administration is likely to be via the lymphatic circulation. The absorption half-life of albiglutide following subcutaneous 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. The elimination half-life of albiglutide is approximately 5 days and steady-state exposures are achieved following 4 to 5 weeks of once-weekly administration. Due to the slow elimination of albiglutide, clinically relevant systemic concentrations may be maintained for up to 4 to 5 weeks following cessation of dosing.

Albiglutide has been shown to bind to the FcRn receptor. The Fc receptor (FcRn), also known as the Brambell receptor, is a MHC class I like molecule that functions to protect IgG and albumin from catabolism.

#### Process 2 to Process 3 Drug Product

Phase II Study GLP114856 was conducted to assess the overall comparability of Process 2 and Process 3 drug product. This study had a single-dose bioequivalence (BE) phase which was used for the PK bioequivalence assessment. Data from the BE phase demonstrated that Process 3 albiglutide is bioequivalent to Process 2 albiglutide, with respect to AUC and Cmax, after a single subcutaneous 30-mg dose (Table 4).

**Table 4: Pharmacokinetic Parameters of Albiglutide (Process 2 and Process 3, Albiglutide Pharmacokinetic Population)**

Parameter	Treatment	n	Geometric LS Means	Ratio of Geometric LS Means	90% CI of Ratio
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	0.927	0.813, 1.056
	Process 3	80	1743		

Source: CSR 114856 Table 13, Page 47. 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.

## 5. Sources of Clinical Data

BLA 125431 was submitted in an electronic Common Technical Document format. At the time of filing, the clinical program investigating albiglutide for type-2 diabetes involved 23 clinical studies (See).

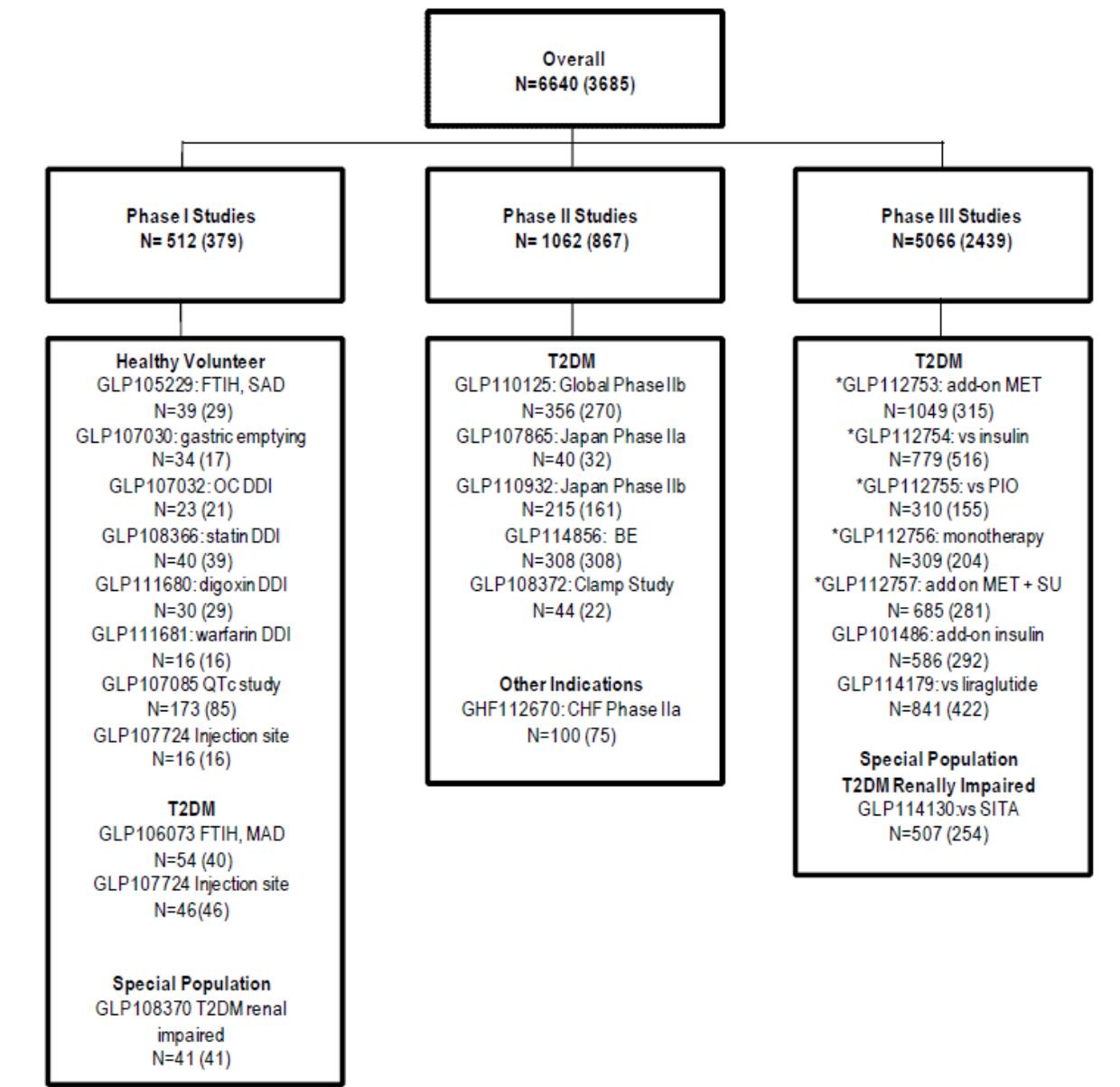
- 10 Phase I studies
- 5 Phase II studies
- 8 Phase III studies

The pivotal efficacy and safety data in support of albiglutide use in subjects with T2DM is derived from seven Phase III studies conducted in a general population of patients with type 2 diabetes (GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP114179, GLP108486). One additional Phase III study (GLP114130) was conducted in subjects with T2DM with various stages of renal impairment (mild, moderate and severe). See Figure 2.

At the time of the BLA submission, three Phase III studies were complete (GLP114179, GLP108486, and GLP114130), and five were ongoing (after having completed the primary endpoint) for assessment of long term efficacy and safety (GLP112753, GLP112754, GLP112755, GLP112756 and GLP115757). All subjects had completed 2 years of treatment at the time of the original BLA submission (data cut-off dates varied by trial).

In addition to the pivotal efficacy and safety studies, one Phase II bioequivalence and clinical comparability study (GLP114856) was conducted to bridge the to-be commercialized drug product (Process 3) with the drug product used in the Phase III program (Process 2). The applicant also conducted two short-term supportive Phase II dose-response studies (GLP110125 and GLP110932).

**Figure 2: Albiglutide Clinical Development Program**



N=All subjects (number of albiglutide treated subjects). BE= bioequivalence; SAD= single ascending dose; CHF = congestive heart failure; DDI= drug-drug interaction; FTIH= first-time-in-human; MAD= multiple ascending dose; MET= metformin; OC= oral contraceptive; OL= open-label; PIO= pioglitazone; SITA= sitagliptin; SU= sulfonyleurea; T2DM= type 2 diabetes mellitus; tQT= thorough QT.

Source: BLA 125431 Clinical Overview, Figure 1, Page 24.

## 5.1 Tables of Studies/Clinical Trials

Table 5 and Table 6 describe the Phase 1 and Phase 2 clinical pharmacology studies conducted in the albiglutide program.

**Table 5: Clinical Pharmacology Phase 1 Trials of Albiglutide**

Study	Short Description of Study	Treatment Details (Drug; Formulation (Process); Form; Frequency; Duration)	Number of Subjects Enrolled (Treatment Groups)
<b>PHASE I CLINICAL PHARMACOLOGY STUDIES</b>			
GLP105229	Single, ascending-dose study in healthy subjects	Albiglutide (Process 1) and Placebo; Subcutaneous injection 30 min prior breakfast on Days 1 and 8; 2 escalating doses per cohort (The actual dose given on each dosing day was determined by PK data from the previous dose levels.) Placebo, 0.25, 1, 3, 6, 16, 24, 48, 60, 80, and 104	39 (10 placebo, 29 albiglutide)
GLP106073	Multiple, ascending-dose study in T2DM subjects	Albiglutide (Process 1) and Placebo; Subcutaneous injection 30 min prior breakfast on Days 1 and 8; 2 doses of albiglutide per dose group (Cohort 1: 9 mg; Cohort 2: 16 mg; Cohort 3: 32 mg)	54 (14 placebo, 40 albiglutide)
GLP107030	Scintigraphy (effect on gastric emptying) study in healthy subjects	Albiglutide (Process 1) or placebo 100 mg single dose SC injection	34 (17 placebo, 17 albiglutide)
GLP107032	Oral contraceptive drug interaction study in healthy female subjects	Albiglutide 50 mg weekly for 4 weeks administered by subcutaneous injection (Process 2); and an oral contraceptive (ethinyl estradiol/ norethindrone [Brevicon])	23 (23 ethinyl estradiol/ norethindrone only, 21 ethinyl estradiol/ norethindrone with albiglutide)
GLP107085	Thorough QTc study in healthy subjects. (Ongoing)	Albiglutide 30 mg (Process 2) weekly for 2 weeks followed by albiglutide 50 mg weekly for 4 weeks, or matching albiglutide placebo administered by subcutaneous injection weekly for 6 weeks; oral dose of moxifloxacin or moxifloxacin matching placebo	173 (88 placebo, 85 albiglutide)
GLP107724	Relative bioavailability and intersubject variability study in healthy and T2DM subjects	Albiglutide (Process 1) Single doses of 16 mg or 64 mg albiglutide via SC on Day 1	62 (62 albiglutide)
GLP108366	Simvastatin drug interaction study in healthy adult subjects	Albiglutide 50 mg weekly for 5 weeks injected subcutaneously beginning on Day 7 (Process 2); and simvastatin single 80-mg oral dose of simvastatin on Day 1 and second single 80-mg oral dose of simvastatin on Day 38	40 (40 simvastatin alone, 39 albiglutide alone, 33 simvastatin with albiglutide)
GLP108370	Single dose study in renally impaired T2DM subjects	Single dose of albiglutide 30 mg (Process 2) administered subcutaneously	41 (10 normal renal function, 11 moderate renal function, 10 severe renal function, and 10 subjects on hemodialysis)
GLP111680	Digoxin drug interaction study in healthy adult subjects	Albiglutide 50 mg weekly for 5 weeks injected subcutaneously (Process 2); and single 0.5-mg oral dose digoxin.	30 (30 digoxin alone, 29 albiglutide alone, 24 digoxin with albiglutide)
GLP111681	Warfarin drug interaction study in healthy male adult subjects	Albiglutide 50 mg weekly for 5 weeks injected subcutaneously beginning on Day 14 (Process 2); and 25 mg oral dose warfarin on Day 1 and a second single 25 mg oral dose of warfarin on Day 45	16 (16 warfarin alone and albiglutide alone, 15 warfarin with albiglutide)

Source: Summary of Clinical Safety (SCS). Modified from Table 1, Page 15-17.

**Table 6: Clinical Pharmacology Phase 2 Trials of Albiglutide**

<b>PHASE II CLINICAL STUDIES</b>			
GLP107865	Multiple, escalating-dose study in Japanese T2DM subjects	Albiglutide (Process 1); 15 mg weekly for 4 weeks, 30 mg weekly for 4 weeks; 50 mg every other week for four weeks (2 doses), 100 mg monthly for 4 weeks (single dose) and Placebo	40 (8 placebo, 32 albiglutide)
GLP108372	Single-site stepped glucose clamp study to assess effects of albiglutide compared to placebo on counter-regulatory hormone responses and recovery from hypoglycemia in T2DM subjects	Placebo; Single dose of albiglutide 50 mg (Process 2)	44 (22 albiglutide, 22 placebo)
GLP110125	Dose-ranging study in T2DM subjects	Albiglutide (Process 1): 4 mg weekly; 15 mg weekly; 30 mg weekly; 15 mg every other week; 30 mg every other week; 50 mg every other week; 50 mg every 4 weeks; 100 mg every 4 weeks; Exenatide (twice daily) and Placebo	356 (51 placebo, 35 exenatide, 270 albiglutide)
GLP110932	Multiple escalating dose study in Japanese T2DM subjects	Albiglutide (Process 2) 15 mg weekly, 30 mg weekly, 30 mg every other week, or placebo weekly for 16 weeks	215 (54 placebo, 161 albiglutide)
GHF112670 (ongoing)	A multi-center, placebo-controlled, study to evaluate the safety of albiglutide and its effects on myocardial metabolism, myocardial function, and exercise capacity in subjects with nonischemic cardiomyopathy and NYHA Class II/III CHF.	Albiglutide (Process 2, pen); 3.75 mg, 15 mg, or 30 mg or matching albiglutide placebo weekly for 14 weeks	76 (27 placebo, 49 albiglutide)
GLP114856	Albiglutide (Process 2) versus albiglutide (Process 3) single dose bioequivalence (BE Phase)	BE Phase: single dose of albiglutide 30 mg (Process 2 and Process 3; 30 mg pens)	BE Phase: 95 randomized (86 treated) to Process 2 and 91 subjects randomized (81 treated) to Process 3
	Albiglutide (Process 2) versus albiglutide (Process 3) single and multiple dose safety, efficacy, trough PK and immunogenicity comparison (Single and Multiple Dose Phase)	Single dose Phase: single dose of albiglutide 30 mg (Process 2 and Process 3, 30 mg pens) Multiple Dose Phase: albiglutide 30 mg weekly for 12 weeks (Week 5 to Week 17) (Process 2 and Process 3; 30 mg pens)	Single and Multiple Dose Phase: 308 subjects total:

Source: Summary of Clinical Safety (SCS). Modified from Table 1, Page 15-17.

The Phase III program includes 8 clinical studies, ranging from 8 months to 3 years in duration, designed to evaluate the efficacy and safety of two doses of once-weekly subcutaneous injections of albiglutide in a broad spectrum of T2DM patients. The clinical program investigated albiglutide as monotherapy, as add-on to single, dual, and triple oral antidiabetic agents, and in combination with insulin glargine. The program also provided both placebo and active comparator data.

Table 7 provides key characteristics of study design and treatment allocation, and number of subjects enrolled for the 8 pivotal phase 3 studies.

**Table 7: Clinical Phase 3 Trials of Albiglutide**

Study	Short Description of Study	Treatment Details (Drug; Formulation (Process); Form; Frequency; Duration)	Number of Subjects Enrolled (Treatment Groups)
GLP112757 (ongoing)	Efficacy and safety of albiglutide + metformin + glimepiride as compared to placebo + metformin + glimepiride or pioglitazone + metformin + glimepiride in T2DM subjects (3 parallel groups)	Metformin + glimepiride + pioglitazone + albiglutide placebo; metformin + glimepiride + pioglitazone placebo + albiglutide placebo); and metformin + glimepiride + pioglitazone placebo + albiglutide (Process 2) 30 mg weekly (with masked up-titration to 50 mg), (disposable pen injector, s.c.)	685 (281 albiglutide + glimepiride + metformin, 288 pioglitazone + glimepiride + metformin, 116 placebo + glimepiride + metformin)
GLP114130	Efficacy and safety of albiglutide as compared with sitagliptin in T2DM subjects with renal impairment	Albiglutide (Process 2) 30 mg weekly (with treatment-masked up-titration to 50 mg weekly, if needed) + sitagliptin matching placebo or albiglutide matching placebo weekly + sitagliptin for 52 weeks	507 (254 albiglutide, 253 sitagliptin)
GLP114179	Efficacy and safety of albiglutide as compared to liraglutide in T2DM subjects [open label]	Albiglutide (Process 2) 30 mg weekly (with treatment up titration to 50 mg weekly at Week 6, disposable pen injector) or liraglutide(0.6 mg daily for the first week followed by an increase in dose to 1.2 mg at Week 1 and an increase in dose to 1.8 mg at Week 2) for 32 weeks	841 (422 albiglutide, 419 liraglutide)
GLP108486	Efficacy and safety of albiglutide + insulin glargine as compared to preprandial lispro insulin + insulin glargine in T2DM subjects [open label]	Albiglutide (Process 2) 30 mg weekly with up-titration to 50 mg if necessary (disposable pen injector, s.c.) + insulin glargine; insulin glargine + preprandial lispro insulin	586 (292 albiglutide + insulin glargine, 294 preprandial lispro + insulin glargine)
GLP112753 (ongoing)	Efficacy and safety of albiglutide + metformin as compared to placebo + metformin, sitagliptin + metformin, or glimepiride + metformin in T2DM subjects (4 parallel groups)	Albiglutide (Process 2) 30 mg weekly with masked up-titration to 50 mg if necessary (disposable pen injector, s.c.) + metformin; sitagliptin + metformin; glimepiride + metformin; metformin + matching albiglutide placebo	1049 (315 albiglutide + metformin, 313 sitagliptin + metformin, 317 glimepiride + metformin, 104 placebo + metformin)
GLP112754 (ongoing)	Efficacy and safety of albiglutide as compared to insulin glargine in T2DM subjects [open label]	Albiglutide (Process 2 and 3) 30 mg weekly with up-titration to 50 mg if necessary, (disposable pen injector, s.c.); insulin glargine	779 (516 albiglutide, 263 insulin glargine)
GLP112755 (ongoing)	Efficacy and safety of albiglutide + pioglitazone as compared to placebo + pioglitazone in T2DM subjects	Pioglitazone or (metformin + pioglitazone) + albiglutide (Process 2) (30 mg weekly, disposable pen injector, s.c.); pioglitazone or (metformin + pioglitazone) + albiglutide matching placebo	310 (155 albiglutide + pioglitazone, 155 placebo + pioglitazone)
GLP112756 (ongoing)	Efficacy and safety of albiglutide as compared to placebo in T2DM subjects who are treatment naive	Albiglutide (Process 2 and 3) 30 mg weekly, disposable pen injector, s.c. (I); albiglutide (Process 2 and 3) 30 mg weekly with up titration to 50 mg weekly after 12 weeks of treatment, disposable pen injector (II); matching albiglutide placebo	309 (102 albiglutide 30 mg, 102 albiglutide 50 mg, 105 placebo)

Source: Summary of Clinical Safety (SCS). Modified from Table 1, Page 17-18.

## 5.2 Review Strategy

Data reviewed are from the original BLA submission and the 120-day safety update to the original BLA. The clinical study report for an additional Phase II study conducted in subjects with congestive heart failure was submitted with the four month safety update and was reviewed for major safety issues.

All phase 3 studies are discussed individually throughout Section 6, Review of Efficacy. Individual study results are presented with respect to the primary and secondary endpoints of interest. When appropriate, studies were grouped together for subgroup analyses. The primary data sources were the individual clinical study reports and the Integrated Summary of Efficacy (ISE).

To assess the safety of Albiglutide, the data from 7 controlled phase 3 studies were considered in an integrated safety dataset. The primary document for the safety review was the Integrated Summary of Safety (ISS). Individual clinical study reports were reviewed for safety data from Study GLP114130 conducted in subjects with renal impairment, and study GHF112670 evaluating albiglutide in subjects with congestive heart failure. In addition safety data from bioequivalence study GLP114865 was reviewed to compare the safety data of Process 2 vs. Process 3 drug substance.

### 5.3 Discussion of Individual Studies/Clinical Trials

The eight Phase 3 studies can be grouped as follows:

- Albiglutide compared with placebo (as monotherapy and on various background therapies)
- Albiglutide compared with *active comparators* (liraglutide, sitagliptin, glimepiride, pioglitazone, and insulin) on various background therapies.
- Monotherapy (GLP114130)
- Add-on to metformin (GLP114179, GLP114130, GLP112754, GLP112753)
- Add on to sulfonylurea (GLP114179, GLP114130)
- Add-on to thiazolidinedione (GLP114179, GLP114130)
- Add-on to metformin plus sulfonylurea (GLP112757)
- Add-on to basal insulin with oral antidiabetic drugs (GLP108486)
- Triple therapy with combinations of metformin, sulfonylurea, and/or thiazolidinedione (GLP114179, GLP114130, GLP112754)

Table 8 provides study details for the 8 pivotal phase 3 studies.

**Table 8: Pivotal Phase 3 Trials for the Type 2 Diabetes Indication**

Study Number	Design	Population	Background Therapy	Treatment Arms	Randomization Treatment [Number of subjects randomly assigned / number completed]	Primary efficacy endpoint time point	Duration of Safety Extension [Total treatment in weeks]
<b>On-going studies</b>							
Compared to Glimepiride and Sitagliptin (add on to Metformin)							
GLP112753	Randomized, double-blind, placebo and active control, multi-center 4 parallel-group	T2DM with inadequate glycemic control on MET <sup>1</sup>	MET (immediate/extended release) ≥1500 mg daily or MTD <sup>1</sup> <1500 mg daily	1. Albiglutide (30 mg weekly, optional uptitration to 50 mg weekly). 2. Glimepiride (2 mg daily, optional uptitration to 4 mg daily). 3. Sitagliptin (100 mg/day). 4. Placebo	3:3:3:1 Albiglutide [315/220] Glimepiride [317/219] Sitagliptin [313/213] Placebo [104/62]	Change from baseline HbA1c to week 104	52 weeks double-blind [156 weeks]
Compared to Insulin Glargine [+/- Metformin (with or without Sulfonylurea)]							
GLP112754	Randomized, open-label active control multi-center 2 parallel-group	T2DM with inadequate glycemic control on MET alone or MET+ SU <sup>1</sup>	MET (immediate/extended release) ≥1500 mg daily or MTD <1500 mg daily +/- SU	1. Albiglutide (30 mg weekly, optional uptitration to 50 mg weekly). 2. Insulin glargine (10 units daily, optional uptitration).	2:1 Albiglutide [516/397] Insulin glargine [263/202]	Change from baseline HbA1c to week 52	104 weeks open-label; [156 weeks]
Add on to Pioglitazone +/- Metformin							
GLP112755	Randomized, double-blind, placebo control, multi-center 2 parallel-group	T2DM, inadequate glycemic control on pioglitazone alone or pioglitazone + metformin	Pioglitazone ≥ 30 mg daily or MTD of 15 mg +/- MET (immediate / extended release) ≥1500 mg daily or MTD <1500 mg	1. Placebo 2. Albiglutide (30 mg weekly, no uptitration).	1:1 Placebo [155/115] Albiglutide 155/133]	Change from baseline HbA1c to week 52	104 weeks; double-blind; [156 weeks]

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			daily				
<b>Monotherapy</b>							
GLP112756	Randomized, double-blind, placebo control, multi-center 3 parallel-group	T2DM drug naïve inadequate glycemic control on diet and exercise	Diet and exercise	1. Placebo 2. Albiglutide (30 mg weekly). 3. Albiglutide (30 mg weekly with forced uptitration to 50 mg weekly at Week 12)	1:1:1 Placebo [105/79] Albiglutide [102/87] Albiglutide (30 mg weekly → 50mg [102/74]	Change from baseline HbA1c to week 52	104 weeks; double-blind; [156 weeks]
Compared to Pioglitazone (add on to Metformin and Sulfonylurea)							
GLP112757	Randomized, double-blind, placebo control, multi-center 3 parallel-group	T2DM, inadequate glycemic control on current regimen of MET or MET + SU <sup>2</sup>	MET (immediate/extended release) ≥1500 mg daily or MTD <1500 mg + open-label glimepiride (4 mg daily)	1. Albiglutide 30 mg weekly, optional uptitration to 50 mg weekly) + Pioglitazone placebo. 2. Pioglitazone 30 mg weekly, optional uptitration to 45 mg weekly) + albiglutide placebo. 3. Placebo (albiglutide and pioglitazone placebo)	5:5:2 Albiglutide [281/220] Pioglitazone [288/223] Placebo [116/80]	Change from baseline HbA1c to week 52	104 weeks; double-blind; [156 weeks]
<b>Completed Studies</b>							
<b>Add on to Insulin Glargine</b>							
GLP108486	Randomized, Open-label active control, multi-center 2 parallel-group	T2DM inadequately controlled on insulin glargine or other intermediate- or long-acting insulins, with or without oral antidiabetic medications	Glargine <sup>3</sup> + other oral agents (MET, TZDs, and alpha-glucosidase inhibitors)	1. Albiglutide (30 mg weekly with optional uptitration to 50 mg weekly + insulin glargine (with uptitration if needed) 2. Lispro insulin + insulin glargine (with uptitration if needed)	1:1 Albiglutide [292/243] Lispro [294/242]	Change from baseline HbA1c to week 26	26 weeks; open-label; [52 weeks]
Compared to Liraglutide							
GLP114179	Randomized, open-label, multicenter 2-	T2DM, inadequate glycemic control	MET, SU <sup>4</sup> and TZD either alone or in	1. Albiglutide (30 mg weekly with uptitration to 50 mg weekly at Week 6)	1:1 Albiglutide [422/346]	Change from baseline HbA1c to	None

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	parallel group	on current background therapy MET, TZDs, or SUs or any combination	combination	2. Liraglutide (0.6 mg daily for the first week increased to 1.2 mg at Week 1 and to 1.8 mg at Week 2)	Liraglutide [419/340]	week 32	
Compared to Sitagliptin in renally impaired subjects							
GLP114130	Randomized, double-blind, active control, multi-center 2 parallel-group	T2DM with renal impairment and inadequate glycemic control on diet /exercise or background therapy of MET, TZDs, or SUs or any combination	Diet & Exercise or MET, TZD and SU <sup>4</sup> either alone or in combination	1. Albiglutide 30 mg weekly, optional uptitration to 50 mg weekly + sitagliptin placebo. 2. Sitagliptin 25, 50 or 100 mg/day per severity of renal impairment+ albiglutide placebo.	1:1 Albiglutide [254] Sitagliptin [253]	Change from baseline HbA1c to week 26	26 weeks; double-blind; [52 weeks]

Source: Clinical Overview Modified from Table 1, Page 28-30 and Integrated Summary of Efficacy (ISE)

<sup>1</sup> MET=metformin, MTD= maximum tolerated dose, TZD= thiazolidinedione, SU=sulfonylurea

All studies with subjects on background metformin-Subjects on background of metformin were on a stable dose of metformin for at least 8 weeks before randomization and should not have received >7 contiguous days of any antidiabetic agents other than metformin within the 3 months before.

<sup>2</sup> GLP112757- Subjects on a sulfonylurea equivalent to 4 mg of glimepiride or subjects taking a dose of glimepiride greater than 4 mg were switched to 4 mg of glimepiride and had an 8-week Run-in/Stabilization Period to stabilize the dose of glimepiride.

<sup>3</sup> GLP108486- Subjects were on background insulin <5 years and ≥20 units per day of a long-acting insulin, unless documented lower MTD. Subjects on other intermediate- or long-acting insulins were switched to insulin glargine. Subjects were continue on their current regimen of oral antidiabetic medications (metformin, thiazolidinediones, and alphasglucosidase inhibitors, with the exception of sulfonylureas, glinides, or dipeptidyl peptidase-IV inhibitors which were discontinued).

<sup>4</sup> GLP114130, GLP114179- subjects with an eGFR <60 mL/min were washed off their metformin dose. For HbA1c <7.5% if the subject was not on a minimal dose of an SU, the SU dose was decreased in half at Visit 2.

### **5.3.1.1. Phase 3 Trial Characteristics:**

At the time of the BLA submission 5 studies were ongoing and 3 were complete. Subjects in the five 156-week ongoing studies (GLP112753, GLP112754, GLP112755, GLP112756 and GLP115757) had a minimum 104 weeks of exposure to study medication. For these five on-going studies subjects continued on their originally assigned treatment for the extension phase. There were four double-blind extensions (GLP112753, GLP112755, GLP112756 and GLP115757) and one open-label extension (GLP112754).

Studies GLP114179, GLP108486, and GLP114130 were complete at the time of submission.

Four Phase III studies had primary endpoints at 52 weeks (Studies GLP112754, GLP115755, GLP112756, and GLP112757) and one at week 104 (Study GLP112753). Studies GLP108486 and GLP114130 had primary endpoints at week 26 and a total study duration of 52 weeks. Study GLP114179 has a primary endpoint and total study duration of 32 weeks.

Five of the 8 Phase III studies were double-blind (GLP112753, GLP112755, GLP112756, GLP112757, and GLP114130) and 3 studies were open-label (GLP112754, GLP108486 and GLP114179)

### STUDY OBJECTIVES

#### Primary Objective:

To demonstrate that albiglutide (as mono or combination-therapy) is safe and effective for the treatment of subjects with T2DM by assessing the effect of albiglutide relative to comparators (placebo or active) on the change in HbA1c from baseline to the primary assessment time points (26, 32 or 104 weeks)..

#### Secondary Objectives:

To determine the change from baseline in HbA1c over time, change from baseline in fasting plasma glucose (FPG), proportion of subjects who achieve an HbA1c treatment goal of <6.5% or <7.0%, time to hyperglycemia rescue and change from baseline in body weight.

### STUDY PERIODS

4 study periods:

- Pre-screening/Screening period of 2 weeks.

- Run-in/Stabilization period of 4 weeks (4-8 weeks in GLP108486 and 6-8 weeks in GLP112757). During the Run-in/Stabilization Period, subjects received placebo injector pens and training on sterile techniques for self-administration at home during the treatment period.
- Treatment Period evaluating efficacy and safety. Assessments performed during the Treatment Period include concomitant medications review, physical examinations, vital sign measurements, triplicate 12-lead ECGs (5 minutes apart), clinical laboratory assessments (including FPG, HbA1c, lipids, insulin, and immunogenicity samples), urinalysis, weight, pregnancy tests, monitor for hyperglycemia, exploratory biomarkers, and review of adverse events and hypoglycemia events. (See Time and Events Table in individual clinical study reports for specific visit schedules and details).
- Post-treatment follow-up period of 8 weeks (16 weeks in GLP112757). Subjects attended a follow-up visit at the end of the 8-week post-treatment period. Assessments performed at the follow-up visit included concomitant medication review, vital sign measurements, safety laboratory assessments (hematology and clinical chemistry), HbA1c, immunogenicity samples, weight, urine pregnancy test, and review of adverse events and hypoglycemia events.

## RANDOMIZATION STRATEGY

Randomization of eligible subjects was stratified by:

- Prior history of myocardial infarction (yes versus no) in all studies
- HbA1c <8.0% or ≥8.0% except study GLP112755 (no HbA1c stratification) and study GLP108486 which used the following stratification criterion HbA1C ≤8.5% vs. >8.5%.
- Age <65 or ≥65 years except GLP108486 (no age stratification)
- Background antidiabetic medication in studies
  - GLP108486 (metformin without TZD, TZD without metformin, both TZD and metformin, or neither TZD nor metformin)
  - GLP112754 (metformin alone versus metformin + sulfonylurea)
  - GLP112755 (with or without metformin) .
- In Renal impairment Study GLP114130, subjects were stratified by severity of renal impairment (mild, moderate, or severe) determined by using the modification of diet in renal disease formula. Eligibility required eGFR to be ≥15 and <90 mL/min. The Modification of Diet in Renal Disease (MDRD) study formula was used to calculate eGFR throughout the study based on the following equation:  $eGFR (mL/min/1.73 m^2) = 175 \times (\text{serum Cr [mg/dL]})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if the subject was female}) \times (1.212 \text{ if the subject was black})$ .

- Severity of renal impairment [mild (eGFR  $\geq 60$  to  $\leq 89$  mL/min), moderate (eGFR  $\geq 30$  to  $\leq 59$  mL/min), severe (eGFR  $\geq 15$  to  $\leq 29$  mL/min)]

#### ROUTE of ADMINISTRATION

Albiglutide was injected subcutaneously into the abdomen, alternating right and left sides of the body

**Reviewer Comment: The applicant's proposed labeling recommends the intended site of subcutaneous injection administration to be in the abdomen, thigh, or upper arm region. Study GLP107724 is a phase 1 study that demonstrated that drug exposure to be comparable following SC administration to the arm, leg, or abdomen in subjects with T2DM.**

#### DOSING STRATEGY

##### Starting Dose

In the Phase III studies the starting dose of albiglutide was 30 mg administered subcutaneously once weekly using a fixed-dose disposable pen injector system. The applicant is proposing the drug product to be supplied as a single use prefilled pen providing 30 or 50 mg of albiglutide.

In Renal study GLP114130 the active comparator sitagliptin was dose based on renal function as described in

**Table 9: Sitagliptin Dose Based on Renal Function**

Renal Function (eGFR)	Sitagliptin Dose
Normal renal function: eGFR $>89$ mL/min/1.73 m <sup>2</sup>	100 mg daily
Mild renal impairment (includes moderate from $>50$ mL/min/1.73 m <sup>2</sup> ): eGFR $\geq 50$ mL/min/1.73 m <sup>2</sup> to 89 mL/min/1.73	100 mg daily
Moderate renal impairment: eGFR $\geq 30$ mL/min/1.73 m <sup>2</sup> to $<50$ mL/min/1.73	50 mg daily
Severe renal impairment: eGFR $<30$ mL/min/1.73 m <sup>2</sup>	25 mg daily

Source: CSR GLP114130 Table 3, Page 51.

eGFR = estimated glomerular filtration rate. Note: The Modification of Diet in Renal Disease study formula was used to calculate eGFR throughout the study based on the following equation:  $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 175 \times (\text{serum Cr [mg/dL]})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$ .

##### Optional Uptitration

Optional uptitration of the albiglutide dose to 50 mg weekly was allowed in studies GLP112753, GLP112754, GLP112757, GLP108486, and GLP114130 if

additional glycemic control was needed. Albiglutide uptitration was allowed one time and was dependent upon tolerability of the 30 mg weekly dose and occurred in a masked manner for the double-blind studies.

If uptitration did not improve glycemic control, rescue medication was permitted at the discretion of the investigator.

#### Forced Uptitration

Two studies included a forced uptitration to 50 mg weekly [GLP112756 (at week12) and GLP114179 (at week 6)].

#### Fixed albiglutide dose (no titration)

Subjects in Study GLP112755 received albiglutide 30 mg weekly with no uptitration.

#### Rescue Treatment

The recommended post rescue treatment was insulin (all studies) and metformin (study GLP112756- the preferred post rescue add-on treatments were metformin or insulin). In studies (i.e., GLP112754 and GLP108486) where glargine was used as a comparator medication or background therapy, prandial insulin was recommended as rescue to achieve glycemic control. Other medications could be added at the investigator's discretion. GLP-1 receptor agonists were prohibited in subjects known to be in the albiglutide treatment group (open label studies). The addition of a dipeptidyl peptidase IV inhibitor (sitagliptin) was discouraged.

Dose Titration and hyperglycemic rescue criteria for the Phase 3 clinical trials are detailed below in Table 10, Table 11, Table 12 and Table 13.

**Table 10: Albiglutide Dose Titration and Hyperglycemic Rescue Algorithm (Studies GLP112753, GLP112754 and GLP 112757)**

Time Interval on Treatment	Dose Titration Condition <sup>3</sup>	Hyperglycemia Rescue Condition
≥Day 1 and <Week 2	No titration	No rescue
≥Week 2 and <Week 4	No titration	A single FPG ≥280 mg/dL <sup>1</sup>
Week 4	A single FPG ≥250 mg/dL <sup>1</sup> and HbA <sub>1c</sub> unchanged or increased from Baseline	A single FPG ≥280 mg/dL <sup>1</sup>
>Week 4 and <Week 12	A single FPG ≥250 mg/dL <sup>1</sup> and HbA <sub>1c</sub> unchanged or increased from Baseline	A single FPG ≥250 mg/dL <sup>2</sup> AND previous titration for ≥4 weeks
≥Week 12 and <Week 24	HbA <sub>1c</sub> ≥7.0% and ≤0.5% reduction from Baseline (GLP112754) HbA <sub>1c</sub> ≥7.5% and ≤0.5% reduction from Baseline (GLP112753 and GLP112757)	HbA <sub>1c</sub> ≥8.5% and ≤0.5% reduction from Baseline AND previous titration for ≥4 weeks
≥Week 24 and <Week 48 (GLP112754 and GLP112757) ≥Week 24 and <Week 104 (GLP112753)	HbA <sub>1c</sub> ≥7.0% (GLP112754) HbA <sub>1c</sub> ≥7.5% (GLP112753 and GLP112757)	HbA <sub>1c</sub> ≥8.5% AND previous titration for ≥4 weeks
≥Week 48 and <Week 143 (GLP112754 and GLP112757) ≥Week 104 and <Week 143 (GLP112753)	HbA <sub>1c</sub> ≥7.0% (GLP112754) HbA <sub>1c</sub> ≥7.5% (GLP112753 and GLP112757)	HbA <sub>1c</sub> ≥8.0% AND previous titration for ≥4 weeks
≥Week 143 and <Week 156	No titration	HbA <sub>1c</sub> ≥8.0% AND previous titration for ≥4 weeks

FPG = fasting plasma glucose, HbA<sub>1c</sub> = glycosylated hemoglobin.

- 15.6 mmol/L. Confirmed by a second sample drawn within 7 days and analyzed by the central laboratory.
- 13.9 mmol/L. Confirmed by a second sample drawn within 7 days and analyzed by the central laboratory.
- Albiglutide uptitration corresponded to an increase from a 30-mg dose once per week to a 50-mg dose once per week.

Source: Summary of Clinical Efficacy (SCE) Table 3, Page 24.

**Table 11: Albiglutide Dose Titration and Hyperglycemic Rescue Algorithm (Study GLP108486)**

Time Interval on Treatment	Dose Titration <sup>1</sup>	Hyperglycemia Rescue
<Week 4	No titration	No rescue
≥Week 4 and <Week 8	No titration	HbA <sub>1c</sub> >9.0 and <0.5 decrease from Baseline
≥Week 8 and <Week 12	HbA <sub>1c</sub> >8.0%	HbA <sub>1c</sub> >9.0 and <0.5 decrease from Baseline
≥Week 12 and <Week 16	HbA <sub>1c</sub> ≥7.5%	HbA <sub>1c</sub> >8.5 and ≥4 weeks since uptitration
≥Week 16 and ≤Week 26	HbA <sub>1c</sub> ≥7.5%	HbA <sub>1c</sub> >8.0% and ≥4 weeks since uptitration
>Week 26 and ≤Week 48	HbA <sub>1c</sub> ≥7.0%	HbA <sub>1c</sub> >7.5% and ≥4 weeks since uptitration

Source: **Summary of Clinical Efficacy (SCE)** Table 5, Page 24.

- Albiglutide uptitration corresponded to an increase from a 30-mg dose once per week to a 50-mg dose once per week.

**Table 12: Dose Titration or Hyperglycemia Rescue (Study GLP114130)**

Time Interval on Treatment	Dose Titration	Hyperglycemia Rescue
≥Day 1 and <Week 2	No titration	No rescue
≥Week 2 and <Week 4	No titration	A single FPG ≥280 mg/dL <sup>1</sup>
Week 4	A single FPG ≥250 mg/dL <sup>1</sup> and HbA <sub>1c</sub> unchanged or increased from Baseline	A single FPG ≥280 mg/dL <sup>1</sup>
>Week 4 and <Week 12	A single FPG ≥250 mg/dL <sup>1</sup> and HbA <sub>1c</sub> unchanged or increased from Baseline	A single FPG ≥250 mg/dL <sup>1</sup> AND previous titration for ≥4 weeks
≥Week 12 and <Week 26	HbA <sub>1c</sub> ≥7.0% and ≤0.5% reduction from Baseline	HbA <sub>1c</sub> ≥8.5% and ≤0.5% reduction from Baseline AND previous titration for ≥4 weeks
≥Week 26 and <Week 48	HbA <sub>1c</sub> ≥7.0%	HbA <sub>1c</sub> ≥8.5% AND previous titration for ≥4 weeks
≥Week 48 and <Week 52	No titration	HbA <sub>1c</sub> ≥8.0% AND previous titration for ≥4 weeks

Source: Clinical Protocol GLP114130 Table 1, Page 36.

FPG = fasting plasma glucose, HbA<sub>1c</sub> = glycosylated hemoglobin. 1. Confirmed by a second sample drawn within 7 days and analyzed by the central laboratory.

**Table 13: Conditions for Hyperglycemic Rescue (Studies GLP112755, GLP112756 and GLP114179)**

Time Interval on Treatment		Hyperglycemia Rescue Condition
GLP112755 and GLP112756	GLP114179	
≥Day 1 and <Week 2	≥Day 1 and <Week 2	No rescue
≥Week 2 and <Week 4 <sup>1</sup>	≥Week 2 and <Week 4	A single FPG ≥280 mg/dL <sup>3</sup>
≥Week 4 <sup>2</sup> and <Week 12	≥Week 4 and <Week 12	A single FPG ≥250 mg/dL <sup>4</sup>
≥Week 12 and <Week 24	≥Week 12 and <Week 26	HbA <sub>1c</sub> ≥8.5% and ≤0.5% reduction from Baseline
≥ Week 24 and <Week 48	≥Week 26	HbA <sub>1c</sub> ≥8.5%
≥Week 48 and <Week 156	-	HbA <sub>1c</sub> ≥8.0%

FPG = fasting plasma glucose.

1. Less than or equal to Week 4 for GLP112755.
2. Greater than Week 4 for GLP112755.
3. 15.6 mmol/L. Confirmed by a second sample drawn within 7 days and analyzed by the central laboratory.
4. 13.9 mmol/L. Confirmed by a second sample drawn within 7 days and analyzed by the central laboratory.

Source: Summary of Clinical Efficacy (SCE) Table 4, Page 23.

## STUDY POPULATION

Albiglutide was studied in men and women with established Type 2 diabetes mellitus. Only adult subjects (i.e. > 18 years of age) were studied. No upper age limit for participation was imposed except in study GLP108486 (see inclusion criteria below).

## INCLUSION and EXCLUSION CRITERIA

### Key common inclusion criteria

1. Male or female (females of childbearing potential practicing adequate contraception)  $\geq 18$  years with type 2 diabetes mellitus experiencing inadequate glycemic control.
  - GLP108486 there was an upper age limit of 75
2. Body mass index (BMI)  $\geq 20$  kg/m<sup>2</sup> and  $\leq 45$  kg/m<sup>2</sup>.
3. HbA1c between 7% and 10% inclusive
  - GLP108486 7% to 10.5%.
4. Baseline fasting C-peptide  $\geq 0.8$  ng/mL ( $\geq 0.26$  nmol/L).
5. Creatinine clearance (eGFR)  $>60$  mL/min (Cockcroft Gault criteria)
  - GLP114130 recruited between eGFR  $\geq 15$  and  $<90$  mL/min/1.73m<sup>2</sup> (Modification of Diet in Renal Disease (MDRD) criteria)
6. Normal thyroid-stimulating hormone level or clinically euthyroid
7. Hemoglobin  $\geq 11$  g/dL (males) and  $\geq 10$  g/dL (females)

### Key common exclusion criteria:

1. History of cancer (except squamous cell or basal cell carcinoma of the skin).
2. History of treated diabetic gastroparesis, ongoing symptomatic biliary disease or history of pancreatitis.
4. History of significant gastrointestinal surgery (gastric bypass/banding, antrectomy, Roux-en-Y bypass, gastric vagotomy, small bowel resection, or surgeries affecting upper gastrointestinal function).
5. Clinically significant cardiovascular and/or cerebrovascular disease including, but not limited to the following:
  - History of stroke or transient ischemic attack within 1 month before screening (subjects deemed clinically stable by the investigator may be enrolled 30 days after the cerebrovascular event).
  - Acute coronary syndrome: Documented MI, any cardiac surgery including percutaneous transluminal coronary angioplasty, coronary stent placement, or coronary artery bypass graft surgery within the 2 months before screening.
  - Unstable angina not responsive to nitroglycerin within the 2 months before screening.
  - Unstable cardiac rhythm (except controlled atrial fibrillation).
  - Current symptomatic heart failure (New York Heart Association class III or IV).
  - Resting systolic pressure is  $>160$  mm Hg and/or diastolic pressure  $>100$  mm Hg. Subject can be treated and rescreened must be on a stable dose of medication for at least 4 weeks before being rescreened.

- Mean QTc interval (Fridericia) >470 ms confirmed by a central reader at Screening.
  - 6. Hemoglobinopathy that may affect determination of HbA1c.
  - 7. History of human immunodeficiency virus infection.
  - 8. History of total bilirubin >1.5 × the upper limit of normal (except history of Gilbert's syndrome and a conjugated bilirubin <35% of total bilirubin).
  - 9. Alanine aminotransferase or aspartate aminotransferase >2.5 × ULN.
  - 10. Fasting triglyceride level >850 mg/dL. If screening triglycerides >500 mg/dL the subject can be treated and on a stable dose of medication for at least 4 weeks prior to rescreening.
  - 11. Acute (within 3 months) hepatitis B infection.
  - 12. History of a psychiatric disorder that will affect the subject participation.
  - 13. History of alcohol or substance abuse within 1 year of screening.
  - 14. Positive urine drug screen result at screening.
  - 15. Female subject is pregnant (confirmed by laboratory testing), lactating, or <6 weeks postpartum.
  - 16. Known allergy to any formulation excipients for albiglutide, history of drug or other allergy (including allergy to (b) (4), or sensitivity to any GLP-1 analogue.
  - 17. Receipt of any investigational drug within the 30 days/ 5 half-lives, current use of GLP1 analogue.
  - 18. History of T1DM, diabetic complications that would preclude participation.
  - 19. Family history of medullary thyroid cancer.
  - 20. Family history of Multiple Endocrine Neoplasia 2.
  - 21. GLP112754\* Hypoglycemia unawareness with autonomic dysfunction.
  - 22. GLP108486\* Hypoglycemia unawareness which has impaired cognitive function and required outside assistance.
- \* Subjects with hypoglycemia unawareness reported either by the subject or identified in medical records taken during the screening process met the exclusion criterion.*

Inclusion criteria for randomization (after the run in/stabilization period)

1. HbA1c between 7.0% and 10.0% (inclusive). The assessment may be repeated weekly for a maximum of 4 additional weeks before randomization. The mean of all HbA1c assessments must be between 7.0% and 10.0% (inclusive) for the subject to be eligible for randomization (except in study GLP108486 the mean HbA1c for randomization eligibility was specified to be at least 7%.)
2. If the mean of the 3 screening ECGs for the QTc interval (Fridericia) is >470 ms, 3 repeat ECGs may be obtained if the mean QTc interval (Fridericia) for all 6 ECGs is ≤470 ms the subject qualifies for entry into the study.
3. If the lipase result is above the ULN then subject will not be randomized. If the amylase result is above the ULN and the lipase below the ULN then isoenzyme analysis will be performed and if pancreatic isoenzyme fraction is not the cause of elevation the subject may continue.

4. GLP108486 subjects switched to insulin glargine at screening should be on a stable dose for at least 2 weeks before randomization. A stable dose of insulin glargine was defined as a +/- 10% dosage change during the 2-week "run-in" period of the trial.

## WITHDRAWAL CRITERIA

### Key common withdrawal criteria

1. Loss to follow-up, termination of study
2. Adverse Events
  - QTc prolongation-mean of 3 centrally read ECGs is >500 ms (or >530 ms for subjects with bundle-branch block or pacemaker,
  - New MI or unstable/accelerated angina
  - Liver stopping criteria (based on centrally measured laboratory values):
    1. ALT  $\geq 3 \times$  ULN and bilirubin  $\geq 2 \times$  ULN (>35% direct bilirubin) (or ALT  $\geq 3 \times$  ULN and international normalized ratio [INR] >1.5 if measured)
    2. ALT  $\geq 8 \times$  ULN
    3. ALT  $\geq 5 \times$  ULN but <8  $\times$  ULN persists for  $\geq 2$  weeks
    4. ALT  $\geq 3 \times$  ULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity
    5. ALT  $\geq 5 \times$  ULN but <8  $\times$  ULN and cannot be monitored weekly for  $\geq 2$  weeks
  - Severe potential allergic reactions
  - Pancreatitis
3. Protocol violation, noncompliance, subject or investigator decision
4. Severe or repeated occurrences of hypoglycemia, which in the investigator's judgment requires withdrawal
5. Pregnancy
6. Development of contraindications for the use of various study medications

**Reviewer Comment: The key inclusion criteria, exclusion criteria and withdrawal criteria are reasonable for assessing the stated study objectives.**

## SAFETY AND TOLERABILITY

### Key Safety and Tolerability Assessments

Subject safety assessments included adverse events (AEs), serious adverse events (SAEs), dropouts, hypoglycemic events, and physical examinations.

Additional safety assessments included evaluation of clinical laboratory evaluations (hematology, chemistry, amylase, lipase, liver enzymes and calcitonin values) 12-lead

electrocardiograms (ECGs), and vital signs (blood pressure and pulse rate) measurements (See safety section 7.4.2 and 7.4.3).

Safety assessments of special interest in the albiglutide program include: CV events, thyroid cancer events, pancreatitis, hypoglycemia events, GI events, potential systemic allergic reactions, diabetic retinopathy and injection site reactions. Details on how these events of special interest were defined, captured and adjudicated can be found in the safety section dedicated to each particular event (See safety section 7.3.4).

Special safety evaluations were presented in the Integrated Analysis of Cardiovascular Risk, Pancreatitis Adjudication Summary Report and Integrated Clinical Immunogenicity Report.

## 6 Review of Efficacy

### Efficacy Summary

The efficacy findings are based on 8 pivotal Phase 3 studies (5 double blinded and 3 open label). Among the 8 Phase 3 trials study GLP114130 was conducted primarily in subjects with renal impairment. The endpoint used to measure treatment effect was the change from baseline in Hemoglobin A1c at each study's primary endpoint (range: 26 to 104 weeks). The primary efficacy population for the individual studies was the Intent-to-Treat (ITT) Population. The ITT subjects were analyzed according to their randomly assigned treatment and missing data was imputed with the last observation carried forward (LOCF). Analysis of data at the primary endpoint demonstrates the statistical superiority of albiglutide to placebo at both the 30 and 50 mg dose. In addition albiglutide was found to be superior compared to sitagliptin and glimepiride. Non-inferiority of albiglutide to pre-prandial insulin lispro and insulin glargine was established. Both liraglutide and pioglitazone were significantly superior to albiglutide.

### 6.1 Indication

The sponsor is seeking an indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Important limitations of use proposed in the label are delineated below.

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise, [REDACTED] (b) (4)
- Has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis.
- Has not been studied in combination with prandial insulin.
- Not [REDACTED] (b) (4) in the treatment of patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis.

## 6.1.2 Methods

Eight Phase 3 pivotal trials were analyzed individually to determine the efficacy of albiglutide (See description in Table 5). The primary efficacy population for the individual studies was the Intent-to-Treat (ITT) population which consisted of all randomized subjects who received at least 1 dose of study medication, had a baseline assessment and at least one post-baseline assessment (scheduled or unscheduled) for the primary endpoint of HbA1c. Missing data was imputed using the last observation carried forward method (LOCF).

### SUBGROUP ANALYSES

Efficacy data from seven of the Phase III Studies (GLP114179, GLP108486, GLP112753, GLP112754, GLP112755, GLP112756 and GLP115757) were integrated to conduct pooled subgroup analyses.

The treatment comparison groupings are described in Table 14.

**Table 14: Efficacy Pooled Study Groups**

Study Number and Pooled Study Groups	Background Medication <sup>1</sup>	Comparator	Visits for Reporting Endpoints (Using LOCF Data)	
			Primary Endpoint at Week	Month 6 (24, 26, 32 weeks)
<i>Study Group A: Albiglutide vs. Placebo Studies</i>				
GLP112753	MET	Placebo	104 <sup>2</sup>	24
GLP112755	TZD (±MET)	Placebo	52	24
GLP112756	--	Placebo	52	24
GLP112757	MET+SU	Placebo	52	24
<i>Study Group B: Albiglutide vs. OAD Studies</i>				
GLP112753	MET	SU DPP-IV	104	24
GLP112757	MET+SU	TZD	52	24
<i>Study Group C: Albiglutide vs. Insulin Studies</i>				
GLP112754	MET (±SU)	Insulin glargine	52	24
GLP108486	Insulin glargine +OAD	Insulin Lispro	26	26
<i>Study Group D: Albiglutide vs. Liraglutide Study</i>				
GLP114179	OAD	Liraglutide	32	32

Source: Integrated Summary of Efficacy (ISE)- Table 5 page 45. DPP-IV = dipeptidyl peptidase IV; LOCF = last observation carried forward; MET = metformin; OAD = oral antidiabetic drug; SU =sulfonylurea; TZD = thiazolidinedione.

1. Background medications are being utilized in all treatment arms of the study.

2. The primary endpoint for Study GLP112753 was Week 104. However, the integrated analysis used week 52 data to ensure alignment with the timing of the other primary endpoints.

### 6.1.3 Demographics

The baseline demographics characteristics for each Phase 3 study are detailed in Table 15. The data represents demographic characteristics combining all treatment groups within each trial. Baseline characteristics between treatment groups within each trial were generally balanced (data not shown; please refer to Dr. Choudhury's statistical review for individual treatment arm baseline characteristics).

The mean age of subjects in the Phase 3 program was 55.9 years and the majority of study participants were in the <65 years age category (80.9% vs. 19%). Overall a comparable proportion of men and women participated in the study (males 51.9% vs. females 48.1%). The mean BMI was 32.6 kg/m<sup>2</sup>.

The ethnic distribution in the combined Phase 3 trial study population consisted of 66.8% white subjects, 11.4% Asians (combined Asian Indian and Asian non-Indian), 14.6% Blacks, and 26.1 % were of Hispanic/Latino heritage across the program.

In the renal impairment study (GLP114130), a higher proportion of subjects (43.6%) were ≥65 years of age. There was also a higher proportion of Central/South and East Asians and a smaller proportion of White/Caucasian/European subjects compared to the other studies. In addition a greater number of subjects had lower mean BMI (<25 kg/m<sup>2</sup>) compared to other studies.

**Table 15: Demographics and Baseline Characteristics of Subjects Enrolled in Albiglutide Phase III Studies**

	GLP112753	GLP112754	GLP112755	GLP112756	GLP112757	GLP108486	GLP114179	GLP114130	TOTAL n (%)
Mean age at randomization (years)	54.5	55.5	55.0	52.9	55.2	55.6	55.6	63.3	55.9 (10.02)
Mean body weight (kg)	90.68	94.91	98.90	96.09	90.79	92.06	92.25	83.04	91.83 (20.723)
<b>Age Category, n (%)</b>									
<65 years	853 (84.3)	626 (84.0)	253 (84.1)	251 (83.4)	548 (82.7)	481 (85.0)	667 (82.1)	279 (56.4)	3958 (80.9)
≥65 years	159 (15.7)	119 (16.0)	48 (15.9)	50 (16.6)	115 (17.3)	85 (15.0)	145 (17.9)	216 (43.6)	937 (19.1)
<b>Sex, n (%)</b>									
Female	530 (52.4)	327 (43.9)	121 (40.2)	135 (44.9)	310 (46.8)	298 (52.7)	403 (49.6)	229 (46.3)	2353 (48.1)
Male	482 (47.6)	418 (56.1)	180 (59.8)	166 (55.1)	353 (53.2)	268 (47.3)	409 (50.4)	266 (53.7)	2542 (51.9)
<b>Race<sup>2</sup>, n (%)</b>									
African American/African Heritage	150 (14.8)	194 (26.0)	39 (13.0)	38 (12.6)	68 (10.3)	73 (12.9)	76 (9.4)	78 (15.8)	716 (14.6)
American Indian or Alaskan Native	73 (7.2)	4 (0.5)	33 (11.0)	5 (1.7)	41 (6.2)	49 (8.7)	68 (8.4)	32 (6.5)	305 (6.2)
Asian - Central/South Asian Heritage	13 (1.3)	12 (1.6)	3 (1.0)	2 (0.7)	20 (3.0)	34 (6.0)	12 (1.5)	78 (15.8)	174 (3.6)
Asian - East Asian Heritage	10 (1.0)	3 (0.4)	5 (1.7)	2 (0.7)	22 (3.3)	32 (5.7)	44 (5.4)	55 (11.1)	173 (3.5)
Asian - Japanese Heritage	2 (0.2)	1 (0.1)	2 (0.7)	1 (0.3)	3 (0.5)	0	3 (0.4)	0	12 (0.2)
Asian - South East Asian Heritage	34 (3.4)	24 (3.2)	2 (0.7)	2 (0.7)	45 (6.8)	32 (5.7)	36 (4.4)	27 (5.5)	202 (4.1)
Native Hawaiian or Other Pacific Islander	2 (0.2)	1 (0.1)	3 (1.0)	6 (2.0)	2 (0.3)	4 (0.7)	2 (0.2)	1 (0.2)	21 (0.4)
White - Arabic/North African Heritage	13 (1.3)	9 (1.2)	5 (1.7)	5 (1.7)	5 (0.8)	5 (0.9)	11 (1.4)	1 (0.2)	54 (1.1)
White - White/Caucasian/European Heritage	723 (71.4)	500 (67.1)	212 (70.4)	242 (80.4)	458 (69.1)	345 (61.0)	562 (69.2)	226 (45.7)	3268 (66.8)
<b>Ethnicity, n (%)</b>									
Hispanic/Latino	349 (34.5)	119 (16.0)	75 (24.9)	85 (28.2)	191 (28.8)	145 (25.6)	241 (29.7)	71 (14.3)	1276 (26.1)
Not Hispanic/Latino	663 (65.5)	626 (84.0)	226 (75.1)	216 (71.8)	472 (71.2)	421 (74.4)	571 (70.3)	424 (85.7)	3619 (73.9)
Mean body mass index (kg/m <sup>2</sup> )	32.58	33.12	34.11	33.52	32.17	33.03	32.79	30.39	32.62

Source: Summary of Clinical Efficacy (SCE): Table 9, Page 40.

Table 16 depicts baseline diabetes characteristics of albiglutide-treated subjects grouped by background therapy.

Baseline HbA1c ranged from 7.85 to 8.48% in the studies. The mean HbA1c for albiglutide treated subjects was 8.22%. The majority of subjects had HbA1c <8% (45.5%) and had diabetes < 10 years. Mean duration of diabetes among albiglutide treated subjects was 8.11 years (4-13 years). There were very few subjects aged 75 or older, and 14.5% were ≥65 to <75 years of age. Renal impairment was present in 62.0% of subjects across treatment groups.

***Reviewer Comment: A higher proportion of subjects on triple therapy and insulin had a longer duration of diabetes and an increasing prevalence of prior MI across the groups. This is not unexpected as subjects generally requiring multiple diabetes medications or insulin likely have more advanced disease.***

**Table 16: Baseline Diabetes Characteristics by Background Treatment (Albiglutide Treated Population)**

	Diet and Exercise (N=197)	Oral Monotherapy (N=578)	Oral Dual Therapy (N=1002)	Oral Triple Therapy (N=34)	Insulin Therapy (N=282)	Total (N=2093)
<b>Weight (kg)</b>						
n	197	578	1002	34	282	2093
Mean (SD)	96.30 (18.756)	90.94 (19.230)	93.69 (20.711)	99.91 (21.315)	92.54 (21.472)	93.12 (20.311)
Median	95.00	89.50	92.15	94.35	91.75	91.40
Minimum, maximum	55.0, 153.8	47.9, 165.9	46.1, 157.9	66.0, 150.0	45.7, 153.7	45.7, 165.9
<b>Body mass index (kg/m<sup>2</sup>)</b>						
n	197	578	1002	34	282	2093
Mean (SD)	33.78 (5.333)	32.78 (5.639)	32.95 (5.732)	34.41 (5.467)	33.15 (6.000)	33.03 (5.707)
Median	34.00	32.00	33.00	35.00	33.00	33.00
Minimum, maximum	21.0, 45.0	20.0, 46.0	20.0, 48.0	23.0, 44.0	21.0, 46.0	20.0, 48.0
<b>Body Mass Index Category (n, %)</b>						
n	197	578	1002	34	282	2093
<25 kg/m <sup>2</sup>	8 (4.1)	29 (5.0)	67 (6.7)	2 (5.9)	17 (6.0)	123 (5.9)
≥25 to <30 kg/m <sup>2</sup>	38 (19.3)	153 (26.5)	235 (23.5)	4 (11.8)	69 (24.5)	499 (23.8)
≥30 to <35 kg/m <sup>2</sup>	60 (30.5)	188 (32.5)	317 (31.6)	10 (29.4)	79 (28.0)	654 (31.2)
≥35 kg/m <sup>2</sup>	91 (46.2)	208 (36.0)	383 (38.2)	18 (52.9)	117 (41.5)	817 (39.0)
<b>Baseline HbA<sub>1c</sub> (%)</b>						
n	197	578	1002	34	282	2093
Mean (SD)	8.13 (0.906)	8.11 (0.865)	8.25 (0.905)	7.85 (0.712)	8.48 (0.923)	8.22 (0.902)
Median	7.90	7.90	8.10	7.75	8.40	8.10
Minimum, maximum	6.5, 10.3	6.8, 11.1	4.9, 12.0	6.7, 9.8	6.5, 11.4	4.9, 12.0
<b>Baseline HbA<sub>1c</sub> Category (n, %)</b>						
n	197	578	1002	34	282	2093
<8.0%	99 (50.3)	295 (51.0)	440 (43.9)	20 (58.8)	98 (34.8)	952 (45.5)
≥8.0% to <9.0%	52 (26.4)	168 (29.1)	320 (31.9)	12 (35.3)	92 (32.6)	644 (30.8)
≥9.0%	46 (23.4)	115 (19.9)	242 (24.2)	2 (5.9)	92 (32.6)	497 (23.7)
<b>Duration of Diabetes (years) <sup>2</sup></b>						
n	197	578	1002	34	282	2093
Mean (SD)	3.80 (4.154)	6.52 (5.085)	8.85 (6.223)	13.23 (8.025)	11.17 (6.520)	8.11 (6.196)
Median	2.26	5.47	7.64	12.43	10.30	6.70
Minimum, maximum	0.0, 29.6	0.1, 35.3	0.3, 41.4	2.8, 35.6	0.6, 30.4	0.0, 41.4

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Prior myocardial infarction (n, %)						
n	197	578	1002	34	282	2093
Yes	5 (2.5)	24 (4.2)	44 (4.4)	3 (8.8)	22 (7.8)	98 (4.7)
No	192 (97.5)	554 (95.8)	958 (95.6)	31 (91.2)	260 (92.2)	1995 (95.3)
Renal status (n, %) <sup>1</sup>						
n	197	578	1002	34	282	2093
Normal (eGFR $\geq$ 90 mL/min/1.73 m <sup>2</sup> )	61 (31.0)	224 (38.8)	376 (37.5)	13 (38.2)	122 (43.3)	796 (38.0)
Renally impaired (eGFR <90 mL/min/1.73 m <sup>2</sup> )	136 (69.0)	354 (61.2)	626 (62.5)	21 (61.8)	160 (56.7)	1297 (62.0)

Source: Integrated Summary of Efficacy (ISE) Table 18, Page 106. eGFR = estimated glomerular filtration rate; ITT = intent-to-treat.

1. Values were calculated using the Modification of Diet in Renal Disease Study Group formula. Subjects were excluded from studies if their creatinine clearance was <60 mL/min using the Cockcroft-Gault method of determining creatinine clearance.
2. To calculate diabetes duration from a partial diagnosis date, a missing month was imputed as January and a missing day was imputed as the first day of the month.

#### 6.1.4 Disposition

Subject disposition in each pivotal Phase 3 study is depicted in Table 17. A minimum of 95.6% of randomly assigned subjects received at least one dose of study drug (Safety Population). Overall discontinuation rates were similar among studies of 52 weeks duration (range 29.5 to 37.1%) and lower in studies of shorter duration (13.8- 23.5% in studies of less than 52 weeks' duration). Discontinuation reasons included adverse events (3.1% - 10.3%), protocol violations (0.3% - 2.3%), noncompliance with the study protocol (1.1% - 4.1%), lost to follow-up (1.6% - 6.8%), and withdrawal of consent to participate (2.6% - 17.8%).

The ITT population was at least 94.4% of the randomized population in each study. Please refer to Dr. Choudury's review for additional details.

*Review Comment:*

*In the open label study GLP108486 a higher proportion of subjects in the albiglutide group discontinued due to adverse events 5.5%, (16/292) vs. comparator lispro 0.7% (2/294). The overall numeric imbalance was primarily due to single event terms. The greatest imbalance between treatment arms was due to injection site reactions with albiglutide (1.1%, 3/285 vs. 0 in lispro).*

*In the open label study GLP112754 a higher number of subjects discontinued treatment due to adverse events in the albiglutide arm vs. insulin glargine (9.1%, 47/516 vs. 2.7%, 7/263). The greatest imbalance (> 3 subjects) was in preferred term events of injection site reactions (2%, 10/44 vs. 0) and nausea (0.8% n=4 vs. 0).*

*In the open label study GLP114179 a higher proportion of subjects in the liraglutide arm (9.8%, 41/419) discontinued due to adverse events compared to albiglutide (7.3%, 31/422).*

*In study GLP112753 more subjects in the placebo arm discontinued overall (40.4%, 42/104) vs. sitagliptin (31.9 %, 100/313), glimepiride (31%, 98/317) and albiglutide (30.2%, 95/315).*

*See Dr. Japobrata Choudhury's review of individual study disposition and see Safety section 7.2.1.*

**Table 17 Disposition of All Subjects Enrolled in Albiglutide Phase III Studies**

Disposition	Clinical Study Disposition, n (%)							
	GLP112753	GLP112754	GLP112755	GLP112756	GLP112757	GLP108486	GLP114179	GLP114130
Randomized population <sup>1</sup>	1049	779	31	309	685	58	84	507
Safety population <sup>1</sup>	1012 (96.5)	754 (95.6)	301 (97.1)	301 (97.4)	663 (96.8)	566 (96.6)	812 (96.6)	495 (97.6)
Discontinued treatment <sup>1</sup>	335 (31.9)	237 (30.4)	91 (29.4)	107 (34.6)	254 (37.1)	81 (13.8)	128 (15.2) <sup>1</sup>	119 (23.5)
Adverse event	51 (4.9)	54 (6.9)	22 (7.1)	24 (7.8)	53 (7.7)	18 (3.1)	72 (8.6)	52 (10.3)
Protocol violation	17 (1.6)	13 (1.7)	7 (2.3)	N/A	11 (1.6)	2 (0.3)	3 (0.4)	5 (1.0)
Noncompliance	34 (3.2)	32 (4.1)	5 (1.6)	8 (2.6)	20 (2.9)	8 (1.4)	9 (1.1)	8 (1.6)
Severe or repeated occurrences of hypoglycemia	1 (0.1)	1 (0.1)	N/A	N/A	N/A	N/A	0	0
Lost to follow-up	40 (3.8)	32 (4.1)	9 (2.9)	21 (6.8)	19 (2.8)	18 (3.1)	16 (1.9)	8 (1.6)
Withdrew consent	156 (14.9)	94 (12.1)	36 (11.6)	40 (12.9)	122 (17.8)	28 (4.8)	22 (2.6)	38 (7.5)
Investigator decision	16 (1.5)	7 (0.9)	4 (1.3)	4 (1.3)	5 (0.7)	2 (0.3)	2 (0.2)	8 (1.6)
Termination of site by sponsor	17 (1.6)	1 (0.1)	5 (1.6)	5 (1.6)	16 (2.3)	4 (0.7)	0	0
Other	21 (3.4)	3 (0.4)	3 (1.0)	5 (1.6)	8 (1.2)	1 (0.2)	4 (0.5)	0
Completed active treatment/continuing in study	677 (64.5)	508 (65.2)	210 (67.7)	194 (62.8)	409 (59.7)	485 (82.8)	686 (81.6)	376 (74.2)
ITT population <sup>1</sup>	999 (95.2)	735 (94.4)	299 (96.5)	296 (95.8)	657 (95.9)	563 (96.1)	805 (95.7)	486 (95.9)
Duration of treatment period	3 years	3 years	3 years	3 years	3 years	52 weeks	32 weeks	52 weeks

Source: Summary of Clinical Efficacy (SCE): Table 8, Page 38. Note: The study treatment durations were as follows: Studies GLP112753, GLP112754, GLP112755, GLP112756 and GLP112757 are all 3-year duration (ongoing with 2-year data reported), Study GLP108486 = 52-weeks, Study GLP114179 = 32 weeks, and Study GLP114130 = 52 weeks.

1. The study populations and discontinued subjects are totals, representing all subjects in all treatment groups.

### 6.1.5 Analysis of Primary Endpoint(s)

The primary endpoint variable for the individual pivotal Phase 3 studies was the mean change from baseline in Hemoglobin A1c (HbA1c) in the intent to treat population (i.e., those subjects who were randomized, treated and had at least one post-baseline HbA1c value).

HbA1c is a validated surrogate endpoint for measuring glycemic control. Ion Exchange High Performance Liquid Chromatography (HPLC) was the methodology for determining HbA1c for all the samples tested in all the phase III efficacy studies. Depending on the country of origin, the samples could have been analyzed at one of four facilities. Each of the HPLC analyzers was validated at the site against known standards. In addition, each analyzer was National Glycohemoglobin Standardization Program (NGSP) Level 1 laboratory certified and traceable to the Diabetes Control and Complications Trial (DCCT) Reference method. Certification at each site was renewed on a yearly basis.

#### STATISTICAL ANALYSIS

The primary efficacy population for the individual studies was the Intent-to-Treat (ITT) Population. This population consisted of all randomized subjects who received at least 1 dose of study medication, had a baseline assessment and at least one post-baseline assessment (scheduled or unscheduled) for the primary endpoint of HbA1c. The ITT subjects were analyzed according to their randomly assigned treatment. Analyses were performed for the ITT population and missing data was imputed with the last observation carried forward (LOCF).

The primary efficacy analysis was conducted using an analysis of covariance (ANCOVA) model with main effects for treatment group, region, history of prior MI (yes versus no), and age category (<65 years versus ≥65 years) and with baseline HbA1c as a continuous covariate. Secondary efficacy variables of fasting plasma glucose and body weight were analyzed using the same ANCOVA model as that used for the primary efficacy variable.

#### INDIVIDUAL STUDY RESULTS

The mean baseline HbA1c in albiglutide treated subjects across studies ranged from 8.05 to 8.47%.

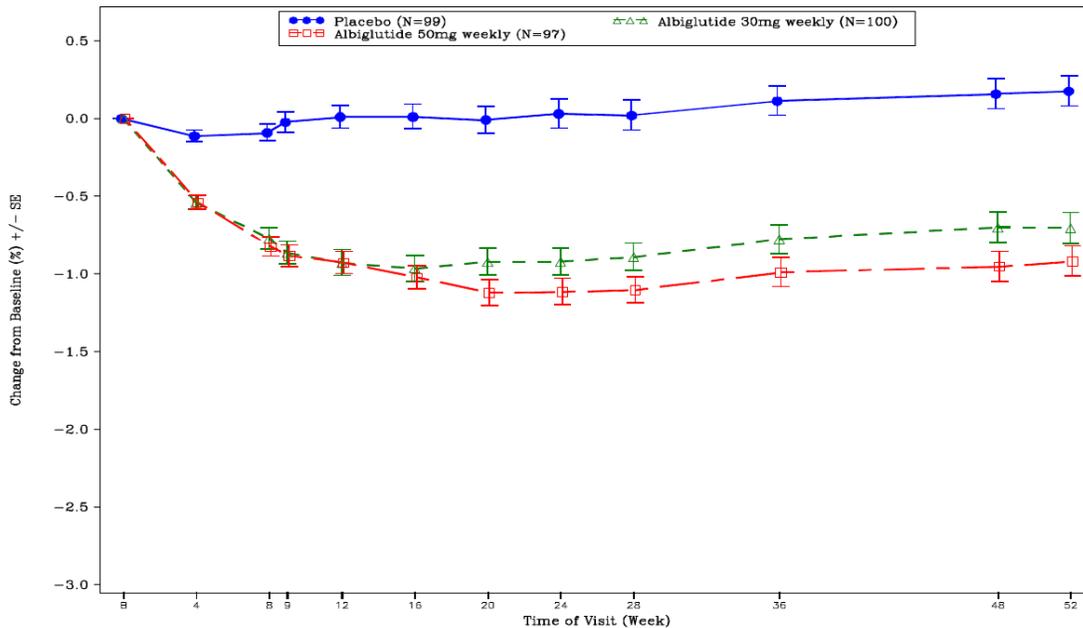
Each trial is discussed individually below and primary efficacy endpoint results are detailed in Table 18.

Monotherapy: Study GLP112756

This study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study designed to evaluate the efficacy and safety of albiglutide 30 mg and 30 mg up-titrated to 50 mg (at week 12) compared with placebo at 52 weeks. The HbA1c treatment effect was evaluated using a sequentially ordered hypothesis strategy. The primary analysis was a superiority analysis comparing albiglutide 50 mg versus placebo followed by superiority testing of albiglutide 30 mg compared to placebo.

The mean baseline HbA1c values were similar across treatment groups. Reductions in HbA1c values from baseline to the primary endpoint (week 52) were observed for both the 30 mg and 50 mg albiglutide treatment arms, while an increase in HbA1c was observed in the placebo group. Model adjusted mean reductions of -0.7% and -0.89% occurred with the 30 mg and 50 mg doses, respectively. Least square mean (LSM) differences demonstrated superiority of albiglutide over placebo with both the 30 mg [-0.84% (95% CI: -1.11, -0.58%)] and 50 mg [-1.04% (95% CI: -1.31, -0.77%)] doses ( $p < 0.0001$ ). Results are depicted graphically in Figure 3.

**Figure 3: Change from baseline HbA1c through week 52 (ITT LOCF)**



Source: CSR GLP112765 Figure 3 page 81

***Reviewer Comment: The efficacy of albiglutide at both the 30 mg and 50 mg are supported by results from the monotherapy study. The HbA<sub>1c</sub> reduction is of statistical significance and clinical relevance. Dr. Choudhury notes that there was a statistically significant quantitative treatment by baseline HbA<sub>1c</sub> (< 8.0, >=8.0) (p=0.0032) interaction, with smaller effects in the <8% group. See statistical review for details.***

#### Add on to metformin: Study GLP112753

This study compared albiglutide to placebo and active comparators sitagliptin and glimepiride added on to background metformin therapy. The HbA<sub>1c</sub> treatment effect was evaluated using a sequentially ordered hypothesis testing strategy. The primary analysis was a superiority analysis of albiglutide versus placebo followed by non-inferiority testing comparing albiglutide to the active comparators. The sponsor had to show that the difference in effect size defined as the change from baseline in HbA<sub>1c</sub> between the two treatment arms at week 104 was no greater than 0.3%. If non-inferiority was established, superiority testing of albiglutide vs. active comparators was conducted.

A decrease in HbA<sub>1c</sub> from baseline to the primary endpoint (week 104) was observed in the albiglutide, sitagliptin and glimepiride treatment groups. Model adjusted mean change in HbA<sub>1c</sub> from baseline was -0.63% in the albiglutide group, -0.28% in the sitagliptin group, -0.36% in the glimepiride group, and +0.27% in the placebo group.

Albiglutide was statistically superior to placebo (-0.91%; 95% CI: -1.16, -0.65, p<0.0001) and non-inferior compared to sitagliptin (-0.35%; 95% CI -0.53, -0.17 p<0.0001) and glimepiride (-0.27%; 95% CI -0.45, -0.09, p<0.0001). Superiority testing demonstrated that albiglutide was superior compared to both sitagliptin (p=0.001) and glimepiride (p=0.0033) at week 104.

#### Add on to pioglitazone +/- metformin: Study GLP112755

The primary objective was to evaluate the efficacy of albiglutide administered in combination with pioglitazone (+/- metformin) as compared to placebo in combination with pioglitazone (+/- metformin) on HbA<sub>1c</sub> change from baseline to week 52.

A reduction in HbA<sub>1c</sub> from baseline to week 52 was observed in both the albiglutide treatment group and placebo. The model-adjusted mean change in HbA<sub>1c</sub> from baseline to the primary endpoint (week 52) was -0.81% in the albiglutide group and -0.05% in the placebo group. The treatment difference (albiglutide - placebo) of -0.75% (95% CI: -0.95, -0.56%) was statistically significant (p<0.0001).

**Reviewer Comment: The distribution of subjects on background pioglitazone and metformin was slightly greater in the albiglutide group compared to placebo (81.3%, 122/150 and 78.1%, 118/151, respectively).**

Add on to metformin and sulfonylurea: Study GLP112757

The study evaluated the HbA1c change from baseline to week 52 of albiglutide compared to placebo and pioglitazone in combination with metformin plus glimepiride. A sequential testing approach was utilized. The first test evaluated the treatment effect by comparing the efficacy of albiglutide to placebo at week 52. If statistical significance was achieved with the placebo, comparison non-inferiority testing to active comparator pioglitazone was conducted (non-inferiority margin of 0.3%). This was followed by superiority testing. If the non-inferiority test was not significant, the superiority test between albiglutide and pioglitazone was not performed.

A decrease in HbA1c from baseline to week 52 was observed in both the pioglitazone and albiglutide treatment groups. The adjusted LS mean change in HbA1c from baseline at Week 52 was -0.55% in the albiglutide group, -0.80% in the pioglitazone group, and 0.33% in the placebo group. The treatment difference for albiglutide - placebo was -0.87% (95% CI: -1.07, -0.68,  $p < 0.0001$ ) and the treatment difference for albiglutide - pioglitazone was 0.25% (95% CI: 0.10, 0.40,  $p = 0.0012$ ) in favor of pioglitazone. Non inferiority was not established.

**Reviewer Comment: This study demonstrated superiority of pioglitazone to albiglutide.**

Add on to insulin glargine: Study GLP108486

This study evaluated the efficacy of albiglutide combined with insulin glargine as compared with the combination of insulin glargine and lispro. A sequential testing approach was utilized that first tested non-inferiority of albiglutide to pre-prandial lispro (non-inferiority limit of 0, 4%). If non-inferiority of albiglutide was established superiority testing was conducted.

A decrease in mean HbA<sub>1c</sub> from baseline to week 26 was observed in both the albiglutide and lispro groups with a greater reduction in the albiglutide arm. The treatment difference for albiglutide – lispro of -0.16% (95% CI: -0.32, 0.00) met the prespecified primary endpoint of non-inferiority to lispro ( $p < 0.0001$ ). However superiority was not established ( $p = 0.053$ ).

Compared to insulin glargine +/- metformin (with or without sulfonylurea): Study GLP112754

This study evaluated the efficacy of albiglutide as compared with insulin glargine in subjects on their current regimen of metformin ( $\pm$  SU). A multiple comparisons adjustment strategy was implemented. The first test evaluated the primary efficacy analysis of HbA<sub>1c</sub> change from baseline at week 52 on treatment comparison using non-inferiority testing (pre-specified non-inferiority margin of 0.3%). If non-inferiority was established superiority testing was conducted.

A decrease in HbA<sub>1c</sub> from baseline to week 52 was observed in both the albiglutide and the insulin glargine treatment groups. The adjusted LS mean change in HbA<sub>1c</sub> from baseline was -0.67% in the albiglutide group and -0.79% in the insulin glargine group. The treatment difference was 0.11% (95% CI: -0.04, 0.27,  $p=0.0086$ ) in favor of glargine and demonstrating non-inferiority of albiglutide to glargine. Superiority was not established ( $p=0.1463$ ).

*As noted in Dr. Choudury's review, non-inferiority of albiglutide to insulin glargine with respect to HbA<sub>1c</sub> was demonstrated by the data (insulin glargine was numerically superior).*

#### Compared to liraglutide: Study GLP 114179

This study evaluated the efficacy of albiglutide compared with liraglutide in subjects with T2DM. First non-inferiority testing (margin of 0.3%) of change from baseline at week 32 in HbA<sub>1c</sub> on the treatment comparison of albiglutide versus liraglutide was conducted. If non inferiority of study drug was established superiority testing to active comparator was performed.

Reductions in HbA<sub>1c</sub> from baseline occurred in both arms, -0.78% with 95% CI of (-0.87, -0.69) and -0.99% with 95% CI of (-1.08, -0.90) for the albiglutide group and the liraglutide group, respectively. The treatment difference for albiglutide minus liraglutide was 0.21% with a 95% CI of (0.08, 0.34). Since the upper bound of the 95% CI was 0.34%, which exceeded the prespecified non-inferiority margin of 0.3%, non-inferiority was not established ( $p=0.0846$ ).

***Reviewer Comment: Dr. Choudhury notes that liraglutide was statistically superior to albiglutide in his analysis.***

#### Compared to sitagliptin in renal impairment: STUDY GLP114130:

This study evaluated the efficacy of albiglutide as compared with sitagliptin in renally impaired subjects with T2DM. A multiple comparisons strategy was implemented with first non-inferiority testing of albiglutide versus sitagliptin (limit 0.3%). If the first test was statistically significant, the next test on treatment comparison of albiglutide versus sitagliptin using superiority testing was conducted.

The model-adjusted LS mean change in HbA<sub>1c</sub> from baseline to week 26 was -0.83% in the albiglutide group and -0.52% in the sitagliptin group. The treatment difference (albiglutide - sitagliptin) was -0.32% (95% CI: -0.49%, -0.15%) establishing non-inferiority to sitagliptin. Superiority testing of the albiglutide versus sitagliptin at week 26 demonstrated statistical superiority to sitagliptin (p=0.0003).

A discussion of albiglutide's efficacy based on severity of renal impairment is detailed in Section 6.2.11.

**Table 18: Summary of changes in HbA<sub>1c</sub> from baseline to the primary endpoint (ITT- LOCF)**

Study # Endpoint (Weeks)	Treatment Arm	N <sup>1</sup>	Baseline HbA <sub>1c</sub> (%) Mean (SD)	LS Mean Change (SE) <sup>2</sup>	LS Mean Difference (95% CI) Albiglutide – Comparator (or placebo) <sup>2</sup>	P value
<b>Monotherapy</b>						
GLP112756 52 weeks	Albiglutide 30 mg	100	8.05 (0.867)	-0.70 (1.009)		
	Albiglutide 50 mg	97	8.21 (0.942)	-0.89 (0.097)		
	Placebo	98	8.02 (0.942)	+0.15 (0.097)	Albiglutide 30 mg: -0.84 (-1.11,-0.58)  Albiglutide 50 mg: -1.04 (-1.31,-0.77)	S;<0.0001  S: <0.0001
<b>Add on to Metformin</b>						
GLP112753 104 weeks	Albiglutide	293	8.09 (0.803)	-0.63 (0.065)		
	Sitagliptin	297	8.06 (0.797)	-0.28(0.065)	-0.35 (-0.53, -0.17)	NI: <0.0001 S: 0.0001
	Glimepiride	299	8.12 (0.843)	-0.36 (0.064)	-0.27 (-0.45, -0.09)	NI: <0.0001 S: 0.0033
	Placebo	97	8.12 (0.887)	+0.27 (0.113)	-0.91 (-1.16, -0.65)	S: <0.0001
<b>Add on to Pioglitazone +/- Metformin</b>						
GLP112755 52 weeks	Albiglutide	149	8.10 (0.955)	-0.81 (0.071)		
	Placebo	149	8.13 (0.851)	-0.05 (0.071)	-0.75 (-0.95, -0.56)	<0.0001
<b>Add on to Metformin and Sulfonylurea</b>						
GLP112757 52 weeks	Albiglutide	265	8.18 (0.908)	-0.55 (-0.65,- 0.44)		
	Pioglitazone	268	8.28	-0.80 (-0.90, - 0.69)	0.25 (0.10, 0.40)	NI: 0.2685
	Placebo	115	8.26	+0.33	-0.87 (-1.07, -	S: <0.0001

				(0.16,0.49)	0.68)	
<b>Add on to Insulin Glargine</b>						
GLP 108486	Albiglutide	279	8.47 (0.924)	-0.82 (0.058)		
26 weeks						
	Lispro	278	8.43 (0.858)	-0.66 (0.058)	-0.16 (-0.32, 0.00)	NI: <0.0001 S: 0.0533
<b>Compared to Insulin Glargine +/- Metformin (with or without Sulfonylurea)</b>						
GLP112754	Albiglutide	493	8.28 (0.9)	-0.67 (0.044)		
52 weeks						
	Lantus	238	8.36 (0.954)	-0.79 (0.064)	0.11 (-0.04, 0.27)	NI: 0.0086 S: 0.1463
<b>Compared to Liraglutide</b>						
GLP114179	Albiglutide	398	8.18 (0.892)	-0.78 (0.047)		
32 weeks						
	liraglutide	402	8.15 (0.841)	-0.99 (0.046)	0.21 (0.08, 0.34)	NI: 0.0846
<b>Compared to Sitagliptin in renally impaired subjects</b>						
GLP114130	Albiglutide	242	8.08 (0.858)	-0.83 (0.062)		
26						
	Sitagliptin	236	8.22 (0.908)	-0.52 (0.063)	-0.32 (-0.49, -0.15)	NI: <0.0001 S: 0.0003

Source Clinical Study Report (CSR): CSR GLP112756 Table 13, page 80, CSR GLP 112753 Table 17, page 90, CSR GLP 112755 Table 13 page 80, CSR GLP112757 Table 13 page 92, CSR GLP108486 Table 18 page 74 , CSR GLP112754 Table 17 page 93, CSR GLP114179 Table 14 page 65, CSR GLP114130 Table 14 page 94.

1. Number of subjects with a value at Baseline and at the specified visit.

2. Based on ANCOVA: Change = treatment + baseline HbA1c + prior myocardial infarction + age category + region + current oral antidiabetic therapy. Difference of least squares means (albiglutide –comparator /or placebo) from ANCOVA model.

NI= non-inferiority p value and S= superiority p value. ANCOVA = analysis of covariance, CI = confidence interval, HbA1c = glycosylated hemoglobin, LOCF = last observation carried forward, LS = least squares, SD = standard deviation, SE = standard error. The HbA1c values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

### 6.1.6 Analysis of Secondary Endpoints(s)

The applicant seeks labeling for secondary endpoints of fasting plasma glucose (FPG), proportion of subjects achieving HbA1c < 7% and body weight. Therefore these 3 endpoints will be the focus of this section. Please see relevant review by Dr. Japobrata Choudhury.

#### FASTING PLASMA GLUCOSE (FPG)

FPG Assay - (b) (4) was the single certified central lab utilized throughout the Phase III clinical program and its validated FPG assay was the standardized assay for all FPG analyses. The fasting plasma glucose assay at (b) (4) utilized the spectrophotometric method (hexokinase/G-6-PDH) measuring the resulting reduced NADH.

As delineated in Table 19, in the monotherapy trial (GLP112756) albiglutide demonstrated a statistically significant reduction in FPG for both the 30 mg and 50 mg

dose levels compared to placebo. Albiglutide exhibited statistically significant superiority to placebo, sitagliptin and glimepiride as measured by change from baseline in FPG at Week 104 (GLP112753). However, albiglutide was statistically inferior to pioglitazone (GLP112757) with respect to FPG.

Both Insulin glargine (Study GLP112754) and Liraglutide (Study GLP114179) were statistically superior to albiglutide with respect to FPG at the primary endpoints. In the renal impairment study (GLP114130) significant differences in FPG were observed in favor of albiglutide ( $p < 0.0001$ ) compared to sitagliptin. Compared to insulin lispro, both arms had decreases from baseline. However, as noted in Dr. Choudhury's review albiglutide was numerically superior.

**Table 19: Summary of changes in Fasting Plasma Glucose (FPG) from baseline to the primary endpoint (ITT- LOCF)**

Study # Endpoint (Weeks)	Treatment Arm	N <sup>1</sup>	Baseline FPG mg/dl Mean (SD)	LS Mean Change (SE) <sup>2</sup>	LS Mean Difference (95% CI) Albiglutide – Comparator (or placebo) <sup>2</sup>	P value
<b>Monotherapy</b>						
GLP112756	Albiglutide 30 mg	100	163.8 (41.6)	-16 (4.26)		
52	Albiglutide 50 mg	97	171.3 (43.2)	-24.8 (4.35)		
	Placebo	99	163.3(42.7)	+18 (4.3)	Albiglutide 30 mg: -34 (-45.9, -22.1)  Albiglutide 50 mg: -42.8 (-54.9, -30.7)	<0.0001  <0.0001
<b>Add on to Metformin</b>						
GLP112753	Albiglutide	296	164.6 (50)	-17.6 (2.9)		
104	Sitagliptin	299	165. (47)	-2.1 (2.88)	-15.5 (-23.5, -7.5)	0.0002
	Glimepiride	302	167.5 (46)	-7.5 (2.87)	-10.1 (-18.1, -2.1)	0.0137
	Placebo	100	162.6 (42)	10.1(4.99)	-27.7 (-39.0, -16.4)	<0.0001
<b>Add on to Pioglitazone +/- Metformin</b>						
GLP112755	Albiglutide	149	165.4 (45.2)	-23.1 (3.55)		
52	Placebo	149	167.1 (47.7)	6.4 (3.55)	-29.5 (-39.4, -19.6)	<0.0001
<b>Add on to Metformin and Sulfonylurea</b>						
GLP112757	Albiglutide	268	170.9 (52.2)	-12.4 (2.86)		
52	Pioglitazone	272	177.3 (56.1)	-31.4 (2.85)	19 (11.1, 26.9)	<0.0001
	Placebo	115	173.8(49.3)	11.5 (4.37)	-23.9 (-34.1, -13.6)	<0.001
<b>Add on to Insulin Glargine</b>						

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GLP 108486	Albiglutide	282	152.5 (54.7)	-17.9 (2.95)		
26	Lispro	279	153.2 (56)	-12.9 (2.96)	-4.9 (-13.2,3.3)	0.2390
<b>Compared to Insulin Glargine +/- Metformin (with or without Sulfonylurea)</b>						
GLP112754	Albiglutide	494	169.4 (51)	-15.7 (2.3)		
52	Lantus	238	175.1 (53.4)	-37.1 (3.31)	21.4 (13.5,29.4)	<0.0001
<b>Compared to Liraglutide</b>						
GLP114179	Albiglutide	400	169.1 (52.5)	-22.1 (2.08)		
32	liraglutide	402	167.1 (48.6)	-30.4 (2.07)	8.3 (2.5, 14.1)	0.0050
<b>Compared to Sitagliptin in renally impaired subjects</b>						
GLP114130	Albiglutide	244	165.5 (58.2)	-25.6 (3.29)		
26	Sitagliptin	240	165 (51.8)	-3.9 (3.32)	-21.7 (-30.9, -12.5)	<0.0001

Source: Clinical Study Report (CSR): CSR GLP112756 Table 14.2-2.1b, page 1729-1740, CSR GLP112753 Table 14.2-2.1b, page 2099-2113, CSR GLP112755 Table 14.2-2.1b page 1571 – 1582, CSR GLP112757 Table 14.2-2.1b page 2070 to 2081, CSR GLP108486 Table 14.2-2.1b, page 1494 to 1502, CSR GLP112754 Table 14.2-2.1b, page 2262 to 2273, CSR GLP114179 Table 14.2-2.1b, page 1258 to 1267, CSR GLP114130 Table 14.2-2.1b, page 1910-1919. 1. Number of subjects with a value at baseline and at the specified visit.  
 2. Based on ANCOVA: Change = treatment + baseline FPG + prior myocardial infarction + age category + region + current oral antidiabetic therapy. Difference of least squares means (albiglutide – comparator/ or placebo) from ANCOVA model. The p-value is from a two-sided t-test for the difference in means.

**Reviewer Comment: Overall fasting plasma glucose results support findings from the primary efficacy endpoint.**

## BODY WEIGHT

In the monotherapy study (GLP112756) the greatest weight reduction occurred in the albiglutide 50 mg group followed by placebo, with the least amount of weight loss in the albiglutide 30 mg arm. Differences in body weight reductions at the primary endpoint favored albiglutide when compared to glimepiride (GLP112753) at week 104.

Subjects on background metformin and sulfonylurea (GLP112755) experienced a greater weight gain in the placebo arm. Pioglitazone increased weight significantly (GLP112757) in subjects on concomitant background of metformin and sulfonylurea.

In active comparator studies against lispro (GLP108486) and glargine (GLP112754) albiglutide resulted in weight loss while each insulin arm experienced weight gain. Liraglutide reduced weight significantly more than albiglutide (GLP114179) and albiglutide reduced weight significantly more than sitagliptin in subjects with renal impairment.

**Table 20: Summary of changes in Body Weight (Kg) from baseline to the primary endpoint (ITT- LOCF)**

Study	Treatment arm	N <sup>1</sup>	Baseline Body weight (kg)	LS Mean (SE) <sup>2</sup>	LS Mean Difference (95% CI) <sup>3</sup>	P value
<b>Monotherapy</b>						
GLP112756	Albiglutide 30 mg	100	95.8 (20)	-0.39 (0.424)		
52	Albiglutide 50 mg	97	96.8 (17.9)	-0.86 (0.432)		
	Placebo	99	95.5 (20)	-0.66 (0.428)	Albiglutide 30 mg: 0.27 (-0.91, 1.46)  Albiglutide 50 mg: 0.20 (-1.40, 1.01)	0.6526  0.7485
<b>Add on to Metformin</b>						
<b>GLP112753</b>	Albiglutide	296	89.61 (18.384)	-1.21 (0.239)		
104	Sitagliptin	300	90.40 (19.046)	-0.86 ((0.237)	-0.35 (-1.10,0.31)	0.2991
	Glimepiride	302	91.88 (20.512)	1.17 (0.237)	-2.37 (-3.03,-1.71)	<0.001
	Placebo	100	91.73 (19.385)	-1.00 (0.411)	-0.20 (-1.14, 0.73)	0.6677
<b>Add on to Pioglitazone +/- Metformin</b>						
GLP112755	Albiglutide	149	97.6 (22)	0.28 (0.348)		
52	Placebo	149	100.2 (23)	0.45 (0.348)	-0.18 (-1.15,0.79)	0.7193
<b>Add on to Metformin and Sulfonylurea</b>						
GLP112757	Albiglutide	268	91.10 (20.174)	-0.42 (0.237)		
52	Pioglitazone	272	91.03 (21.238)	4.43 (0.235)	-4.85 (-5.51, -4.20)	<0.001
	Placebo	115	89.90 (18.820)	-0.40 (0.362)	-0.03 (-0.88, 0.82)	0.9499
<b>Add on to Insulin Glargine</b>						
GLP 108486	Albiglutide	282	92.54 (21.472)	-0.73 (0.194)		
26	Lispro	280	91.59 (20.991)	0.81 (0.195)	-1.54 (-2.09, -1.00)	<0.0001
<b>Compared to Insulin Glargine +/- Metformin (with or without Sulfonylurea)</b>						
GLP112754	Albiglutide	495	95.23 (19.571)	-1.05 (0.171)		

52	Lantus	238	94.64 (19.091)	1.56 (0.247)	-2.61 (-3.2, -2.02)	<0.0001
<b>Compared to Liraglutide</b>						
GLP114179	Albiglutide	400	91.54 (21.274)	-0.64 (0.182)		
32	liraglutide	402	92.94 (22.202)	-2.19 (0.182)	1.55 (1.05, 2.06)	<0.0001
<b>Compared to Sitagliptin in renally impaired subjects</b>						
GLP114130	Albiglutide	244	83.69 (19.846)	-0.79 (0.192)		
26	Sitagliptin	240	82.73 (20.633)	-0.19 (0.194)	- 0.60 (-1.14, - 0.06)	0.0281

Source: Clinical Study Report (CSR): CSR GLP112756 Table 24 page 108, CSR GLP112753 Table 30 page 120, CSR GLP112755 Table 24 page 106 , CSR GLP112754 Table 29 page 118, CSR GLP114179 Table 25 page 85, CSR GLP114130 Table 27 page 121, CSR GLP108486 Table 29 page 95, CSR GLP112757 Table 21 page 110.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline weight + prior myocardial infarction history + age category + region + current antidiabetic therapy.
3. The difference of least squares means (albiglutide – comparator/ or placebo) was from the ANCOVA model. The p-value was from a 2-sided t test for the difference in means.

**Reviewer Comment: At the primary endpoint the change in mean change in body weight ranged from +0.28 kg to -1.21 kg. Subjects in the pioglitazone arm (GLP112757) had the greatest overall weight gain (4.43 kg at week 52). The change in body weight (+0.28 kg) when adding albiglutide to background pioglitazone (GLP112755) suggests that the background pioglitazone therapy may attenuate the weight reduction with albiglutide. Attenuation of albiglutide weight loss was not noted with background sulfonylurea and insulin use (both associated with weight gain).**

### 6.1.7 Other Endpoints

#### SUBJECTS ACHIEVING HbA1c < 7%

More subjects on albiglutide met HbA1c levels < 7% when compared to placebo. The percent of subjects achieving glycemic target goals is summarized in Table 21 below. A greater percentage of patients on albiglutide achieved glycemic target by the end of study when compared to placebo and sitagliptin.

**Table 21: Analysis of Proportion of Subjects Achieving Clinically Meaningful HbA1c Response Levels (<7.0%) at the Primary Endpoint (ITT Population – LOCF)**

Study	Treatment arm	N <sup>1</sup>	HbA1c level: <7.0% N (%)
<b>Monotherapy</b>			
GLP112756	Albiglutide 30 mg	100	39 (40.2)
52	Albiglutide 50 mg	97	49 (49.0)
	Placebo	98	21 (21.4)
<b>Add on to Pioglitazone +/- Metformin</b>			
<b>GLP112753</b>	Albiglutide	293	113 (38.6)
104	Sitagliptin	297	94 (31.6)
	Glimepiride	299	94 (31.4)
	Placebo	97	15 (15.5)
<b>Add on to Metformin and Sulfonylurea</b>			
GLP112755	Albiglutide	149	66 (44.3)
52	Placebo	149	22 (14.8)
<b>Add on to Metformin and Sulfonylurea</b>			
GLP112757	Albiglutide	265	79 (29.8%)
52	Pioglitazone	268	94 (35.1%)
	Placebo	115	10 (8.7%)
<b>Add on to Insulin Glargine</b>			
GLP 108486	Albiglutide	279	83 (29.7)
26	Lispro	278	70 (25.2)
<b>Compared to Insulin Glargine +/- Metformin (with or without Sulfonylurea)</b>			
GLP112754	Albiglutide	493	156 (31.6)
52	Lantus	238	78 (32.8)
<b>Compared to Liraglutide</b>			
GLP114179	Albiglutide	398	168 (42.2)
32	liraglutide	402	208 (51.7)
<b>Compared to Sitagliptin in renally impaired subjects</b>			
GLP114130	Albiglutide	242	103 (42.6)
26	Sitagliptin	236	72 (30.5)

Source: Clinical Study Report (CSR): CSR GLP112757 Table 19, Page 107. CSR Table CSR GLP112755 Table 22, Page 102. CSR GLP 112756 Table 22 Page 102, CSR GLP112753 Table 28 Page 116, CSR GLP108486 Table 27 page 91, CSR GLP112754 Table 27 page 114 CSR glp114130 table 25 page 117, CSR glp114179 Table 23, page 80

1. Number of subjects with a value at the specified visit.

### 6.1.8 Subpopulations

Please see review by Dr. Choudhury for individual study subpopulation efficacy analyses. This review focuses on pooled data from placebo controlled Phase 3 trials. The adjusted (for treatment group, baseline HbA1c, history of prior MI, age category, region, and study) least square mean change in HbA1c from baseline in the albiglutide group at week 52 was -0.71% (N=913) compared with 0.14%(N=416) in the pooled

placebo group . The treatment difference for albiglutide minus placebo at week 52 was -0.86% (95% CI: -0.96, -0.75).

**Table 22: Analysis of Change From Baseline in HbA<sub>1c</sub> (%) Across Study Groups (ITT Population - LOCF)**

	Group A	
	Placebo (N=463)	Albiglutide (N=913)
<b>Week 52</b> <sup>1</sup>		
Number of subjects <sup>2</sup>	459	904
Number (%) of values carried	279 (60.8)	300 (33.2)
Baseline mean (SD)	8.13 (0.905)	8.13 (0.882)
Primary endpoint mean (SD)	8.26 (1.206)	7.43 (1.074)
Change from Baseline mean (SD)	0.12 (0.901)	-0.70 (0.951)
Model-adjusted change from Baseline <sup>3</sup>		
LS mean (SE)	0.14 (0.042)	-0.71 (0.030)
95% confidence	0.06, 0.23	-0.77, -0.65
Difference from		
Difference of LS		-0.86
95% confidence		-0.96, -0.75

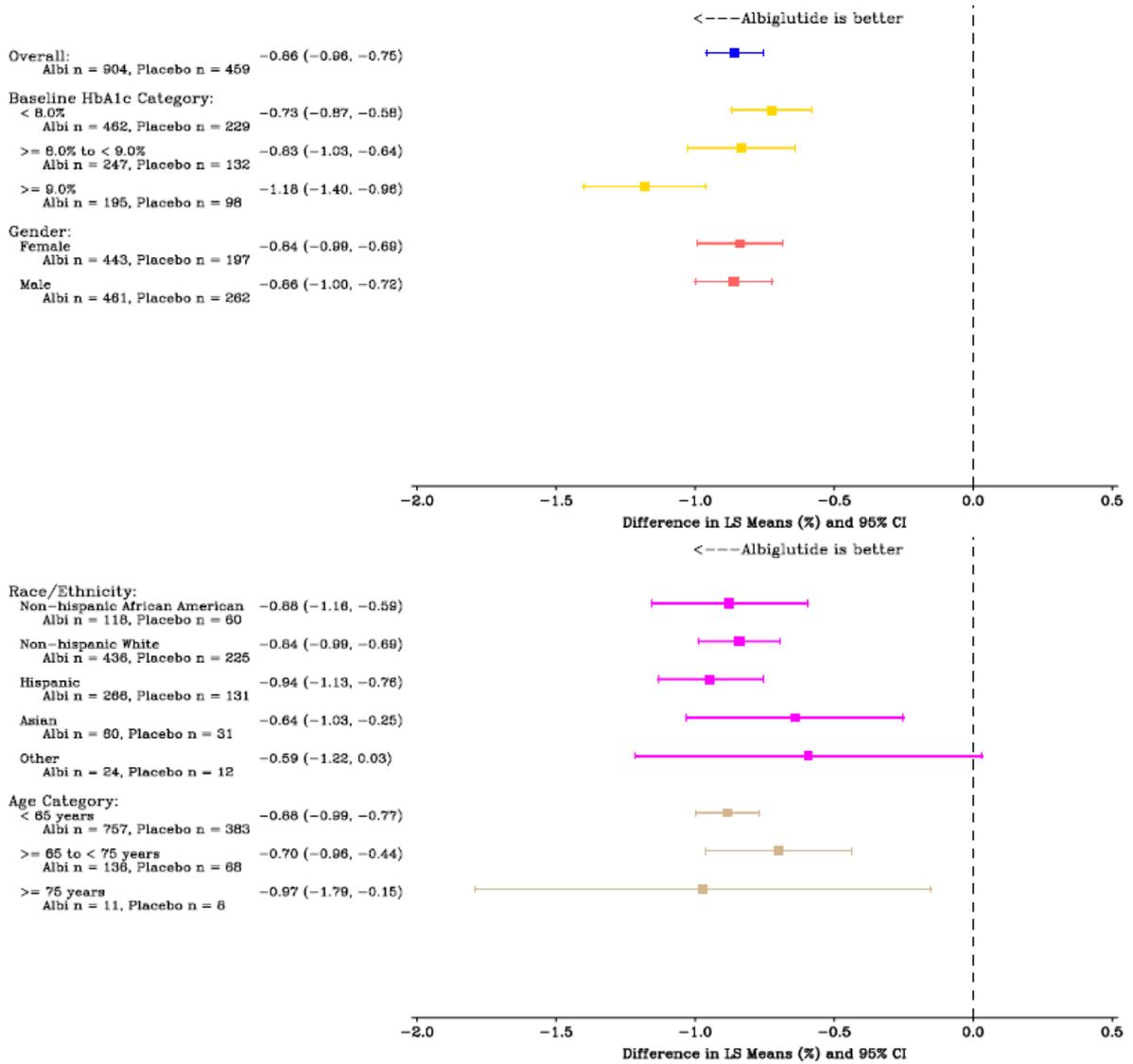
1. This is the primary endpoint for Study Groups A (GLP112753, GLP112755, GLP112756, GLP112757).

2. Number of subjects with a value at Baseline and at the specified visit is displayed.

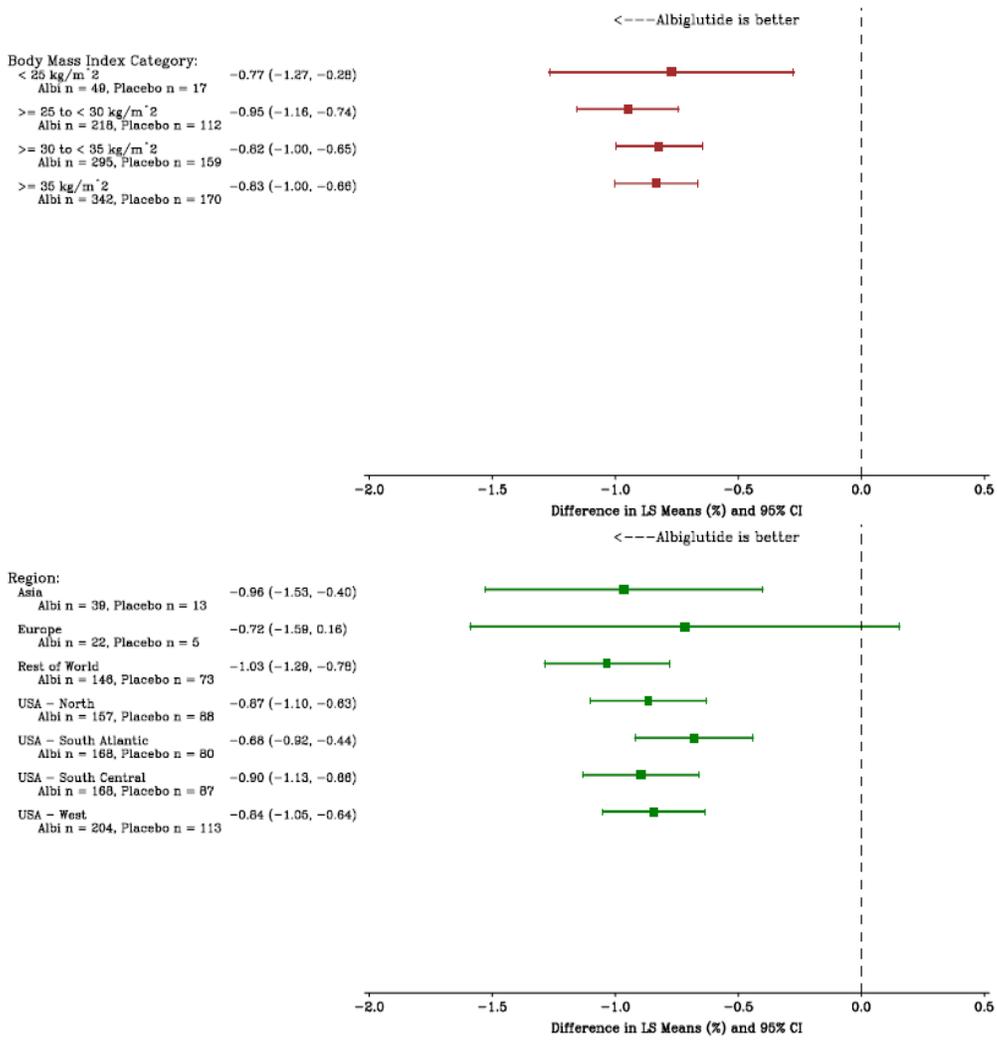
3. Based on ANCOVA: Change = treatment + baseline HbA<sub>1c</sub> + prior myocardial infarction history + age category + region + study. The difference of least squares means (albiglutide - comparator) is from the ANCOVA model.

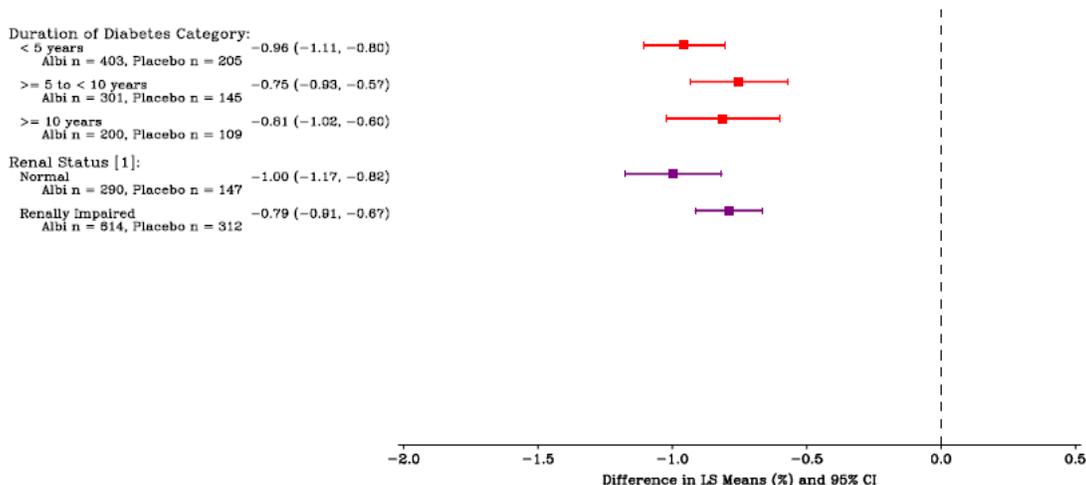
Forest plots of adjusted mean difference in change from Baseline in HbA<sub>1c</sub> by subgroup category are depicted in Figure 4. The positive treatment difference for albiglutide - placebo was demonstrated across subgroups of 3 age categorizes ( $\geq 65$  to  $< 75$  years and  $\geq 75$  years), both genders, all race/ethnic groups, BMI, duration of diabetes, region and renal status. A greater magnitude reduction in HbA<sub>1c</sub> was noted in subjects with baseline HbA<sub>1c</sub> level  $> 9\%$  [-1.18 ; 95% CI (-1.4,-0.96)] compared to  $< 8\%$  [-0.73; 95% CI (-0.87, -0.58)].

**Figure 4: Forest Plot of Model-Adjusted Mean Difference in Change From Baseline in HbA1c (%) Between Albiglutide and Placebo at Primary Endpoint by Subgroup Category (Intent-to-Treat Population, - LOCF)**



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Source Data: Figure E1.1.

Albi = albiglutide; CI = confidence interval; HbA<sub>1c</sub> = glycosylated hemoglobin; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; USA = United States of America.

Note: Week 52 data are presented as the primary endpoint for all studies in Group A.

1. Normal is defined as eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>; renally impaired is defined as  $< 90$  mL/min/1.73 m<sup>2</sup> (MDRD Study Group formulae). Subjects were excluded from studies if creatinine clearance was  $< 60$  mL/min using the Cockcroft-Gault method of determining creatinine clearance.

Source: Integrated Summary of Efficacy (ISE) Figure 24 page 143

### 6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Two Phase IIB dose-finding studies (GLP110125 and Study GLP110932) were conducted in T2DM subjects evaluating varying doses and regimens of albiglutide compared with placebo over a 16-week treatment period. In study GLP110125, 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. In study GLP110932, albiglutide was administered to Japanese subjects once weekly (15 mg, 30 mg), or every other week (30 mg) for 16 weeks.

Study GLP110125 demonstrated that the 30 mg once weekly dose was well-tolerated and produced a clinically relevant reduction in HbA<sub>1c</sub> at week 16 (see Table 23). Higher doses were also tested in other Phase II studies. Based on some increase in efficacy with increased doses and PK/PD modeling of the 50mg dose it was postulated that a subset of subjects would benefit from this higher dose.

Efficacy of the 30 mg dose was demonstrated in the Phase 3 clinical program as described previously in Section 6.1.5. Study GLP112756 demonstrated the benefit of albiglutide 30 mg and 50mg weekly on HbA<sub>1c</sub> reduction. Both study GLP112756 and GLP114179 demonstrated the benefit of uptitration to 50 mg.

**Table 23: Mean Decrease From Baseline HbA<sub>1c</sub> (%) in Albiglutide Efficacy Studies**

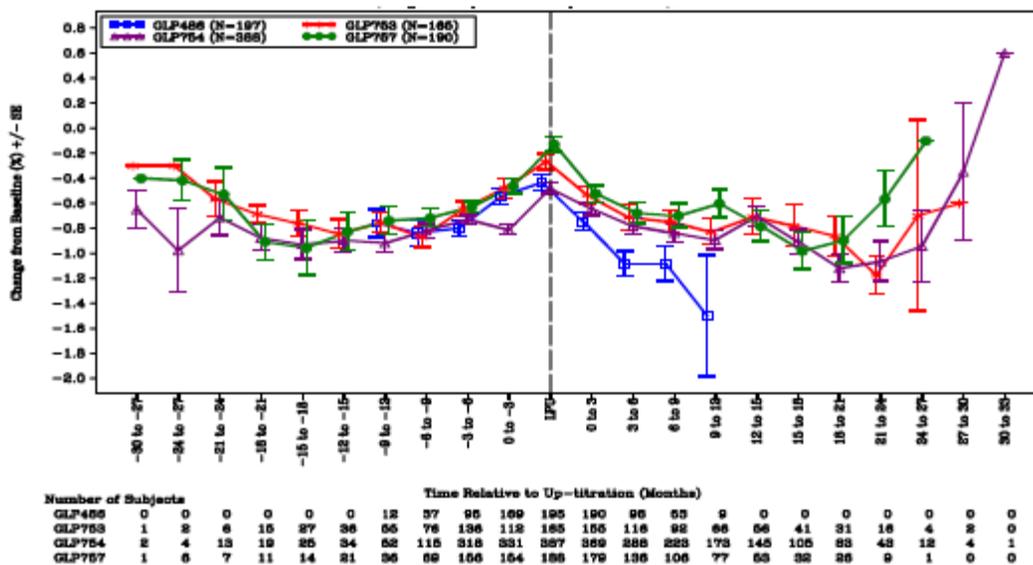
Study #	Albiglutide (N = ITT Population)	Mean HbA <sub>1c</sub> Decrease From Baseline		P-Value at Primary Endpoint
		Primary Endpoint	Secondary Endpoint	
<b>Primary Efficacy Studies</b>				
GLP112756	100 (30 mg) 97 (50 mg)	-0.70% at Week 52 (30 mg) -0.89% at Week 52 (50 mg)	-0.90% at Week 104 -1.05% at Week 104 3-yr data in progress	<0.0001 vs. placebo
GLP112757	269	-0.55% at Week 52	-0.83% at Week 104 3-yr data in progress	<0.0001 vs. placebo
GLP114179	402	-0.78% at Week 32	N/A	0.0846 vs. liraglutide
<b>Supportive Efficacy Studies</b>				
GLP110125	29 <sup>1</sup>	-1.08% at Week 16 (30 mg)	N/A	0.0027 vs. placebo
GLP110932	54 <sup>1</sup>	-1.27% at Week 16 (30 mg)	N/A	<0.0001 vs. placebo

Modified from Integrated Summary of Efficacy (ISE) Table 43 Page 202. HbA<sub>1c</sub> = glycosylated hemoglobin; N/A = not available; q.d. = once per day.

1. For studies GLP110125 and GLP110932, N=number of subjects randomized to 30 mg albiglutide.

Four studies (GLP108486, GLP112753, GLP112757, and GLP112754) had optional uptitration of albiglutide from 30 mg weekly to 50 mg weekly if the subject met the protocol-defined uptitration criteria. Week 52 mean HbA<sub>1c</sub> decreases from baseline in subjects who did not require rescue therapy were -0.73% to -0.75% when subjects were up titrated between weeks 12 and 24. Figure 5 graphically depicts the benefit in HbA<sub>1c</sub> reduction with dose uptitration in the optional uptitration studies.

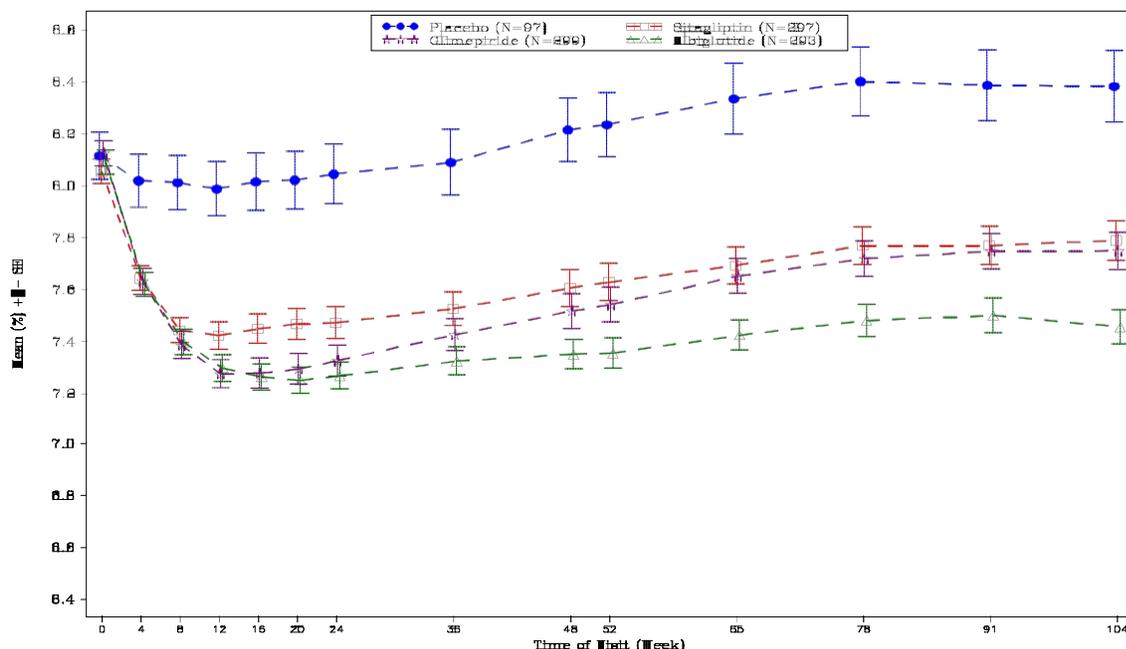
**Figure 5: Mean Change from Baseline in HbA1c (%) Relative to Time of Uptitration Excluding Post rescue Values (Albiglutide Up titrated Population)**



**6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects**

The applicant assessed albiglutide’s glycemic durability in Study GLP112753, which evaluated albiglutide compared with sitagliptin, glimepiride and placebo in subjects failing metformin at the primary efficacy endpoint at week 104. As depicted in Figure 6, albiglutide demonstrated durable efficacy in change from baseline in HbA<sub>1c</sub> at Week 104 compared to all the treatment groups. As demonstrated in the graph, there was a loss of efficiency in the sitagliptin and glimepiride arm after week 24. In addition fewer subjects in the albiglutide group required hyperglycemic rescue (21.2%) compared to subjects randomly assigned to receive placebo (45.0%), sitagliptin (30.0%) or glimepiride (26.5%). The median time to hyperglycemic rescue was 67.71 weeks for the placebo group, 130.43 weeks for both the sitagliptin and glimepiride groups and 132 weeks for the albiglutide group.

**Figure 6: Mean HbA<sub>1c</sub> (%) Through Week 104 (ITT Population – LOCF for Missing and Post rescue Values) Study GLP112753**



Source: CSR GLP112753, Figure 6.  
 HbA<sub>1c</sub> = glycosylated hemoglobin; LOCF = last observation carried forward; SE = standard error.

### 6.1.11 Additional Efficacy Issues/Analyses

This section focuses on efficacy issues pertaining to albiglutide antibody status, background therapy and severity of renal impairment.

#### EFFICACY AND ALBIGLUTIDE ANTIBODY STATUS

##### Pooled Phase 3 Studies

The impact of anti-albiglutide antibodies on efficacy was assessed via pooled data from 7 Phase III studies (GLP112753, GIp112754, GLP112755, GLP112756, GLP114179, GLP108486, GLP112757). There were 116 subjects who tested positive for anti-albiglutide antibodies at 1 or more time points post baseline (including 9 subjects with preexisting anti-albiglutide antibodies) and 1925 who were antibody negative.

Change in HbA<sub>1c</sub> at the primary endpoint was analyzed by antibody status, and found to be similar for antibody positive and antibody negative subjects [-0.72% vs. -0.71%, respectively, (See clinical Immunogenicity report Table 66, Page 61)]. The change from

baseline in HbA1c at the primary endpoint was comparable between all 3 anti-albiglutide antibody titer groups.

One subject with positive pre-existing antibodies tested weakly positive for neutralizing antibodies. However when compared to baseline, the mean change in HbA1c from baseline was -2.9%.

#### Renal Study (GLP114130)

The applicant notes that anti albiglutide antibodies developed in 3% (6/231) of albiglutide treated subjects. The mean (+/-SD) change in HbA1c at the primary endpoint (week 26) was -0.36 (+/-1.14) for antibody-positive subjects and -0.83 (+/-0.89) for antibody-negative subjects. The applicant notes that there did not appear to be a correlation between anti-albiglutide titers and change in HbA1c at the primary endpoint.

*Review Comment: The small sample size in the renal study limits determination of any conclusions. In general the development of anti-albiglutide antibodies in the Phase 3 clinical program did not appear to impact the efficacy of albiglutide.*

#### BACKGROUND THERAPY

The effect of albiglutide on HbA1c based on background therapy demonstrated the largest decreases in HbA1c at 6 and 12 months occurred in subjects on background of only diet and exercise (-1.02% and -0.81% at 6 and 12 months, respectively n=197). The smallest decrease in HbA1c occurred in subjects whose background therapy was oral triple therapy (-0.52%, data are available only for 6 months, n=34). See Table 42 ISE Page 197.

***Reviewer Comment: It is not unexpected that subjects with presumably more advanced disease requiring multiple antidiabetic medications would have less of a reduction in HbA1c.***

#### RENAL STATUS

Study GLP114130 evaluated the efficacy of albiglutide in subjects with T2DM who had mild, moderate, and severe renal impairment (i.e., eGFR  $\geq 15$  and  $< 90$  mL/min/1.73 m<sup>2</sup>). Overall 57% of subjects in the albiglutide group up-titrated from 30 mg weekly to 50 mg weekly [mild (53%, n=69/128), moderate (60%, n=61/102) and severe (58%, n=11/19) renal impairment subgroups].

#### HbA1c

As depicted in Table 24 the model adjusted change from baseline at week 26 was greater in the albiglutide group for all 3 categories of renal impairment when compared to sitagliptin. The treatment difference at week 26 (albiglutide - sitagliptin) was -0.13

(95% CI: -0.37, 0.11), -0.53 (95% CI: (-0.80, -0.26), and -0.47 (95% CI: -1.12, 0.18) for subjects with mild, moderate or severe renal impairment, respectively.

**Table 24: 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 <sup>1</sup>	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)
<b>Model-adjusted change from Baseline<sup>2</sup></b>						
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)
<b>Difference from sitagliptin<sup>2</sup></b>						
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: CSR 114130 Table 19 Page 106

CI = confidence interval; HbA<sub>1c</sub> = 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 post baseline HbA<sub>1c</sub> values. The HbA<sub>1c</sub> 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<sub>1c</sub> + 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.

### Fasting Plasma Glucose (FPG)

At week 26, the difference of LS means in FPG (albiglutide – sitagliptin) was -0.83 mmol/L, -1.60 mmol/L and -1.56 mmol/L for subjects with baseline renal impairment severity of mild, moderate or severe, respectively

### Weight

At week 26, the adjusted LS mean weight change from baseline was -0.79 kg for albiglutide subjects and -0.19 kg for sitagliptin subjects (p=0.0281). The treatment

difference in body weight (kg) at week 26 (albiglutide - sitagliptin) was  $-0.31$  (95% CI:  $-1.06, 0.44$ ),  $-0.94$  (95% CI:  $-1.79, -0.10$ ), and  $-0.74$  (95% CI:  $-2.72, 1.23$ ) for subjects with mild, moderate, or severe renal impairment, respectively

#### HbA1c goal <7%

A higher percentage of subjects in the albiglutide treatment group achieved the treatment goal of HbA1c <7.0% at week 26 (42.6% vs 30.5%, respectively).  
respectively)

***Reviewer Comment: Dr. Chowdhury notes that there were statistically significant quantitative treatment by gender ( $p=.053$ ) and by renal Impairment (.086) interactions. See statistical review for details.***

#### BIOEQUIVALENCE STUDY

Study GLP114856 is a randomized, double-blind, multicenter, 2 parallel-group study in subjects with T2DM designed to show the clinical comparability of Process 2 and Process 3 albiglutide.

This study had a single-dose phase (BE phase) that was used for the comparative PK assessment of Process 2 versus Process 3 albiglutide. Subjects completing the bioequivalence phase continued in the repeat-dose phase that evaluated Process 2 and Process 3 with regard to glycemic effect (e.g., HbA<sub>1c</sub>, FPG), immunogenicity, and safety.

Subjects with T2DM whose glycemia was inadequately controlled on their current regimen of diet and exercise or stable dose of metformin maintained for approximately 8 weeks prior to screening were recruited into the study. Subjects continued on their current regimen of diet and exercise or stable dose of metformin for the duration of their participation in the study. A 30 mg dose of Process 2 and Process 3 albiglutide was administered once weekly for 12 weeks to confirm that there were not clinically relevant differences between Process 2 and Process 3 albiglutide with respect to safety, tolerability, immunogenicity, and glycemic effect ( HbA1c, fasting plasma glucose).

The main efficacy objectives were to evaluate the efficacy of 30 mg of albiglutide (from Process 2 relative to Process 3) drug product administered weekly on HbA1c change from baseline at week 17 and on FPG change from baseline at week 17

A decrease in HbA1c from baseline to week 17 was observed in both treatment groups. When adjusted for baseline HbA1c, age category, weight category and background antidiabetic therapy category, the model adjusted LS mean change in HbA1c from baseline at week 17 was -0.75% in the Process 2 treatment group, and -0.84% in the Process 3 treatment group. The treatment difference for Process 3 - Process 2 was -

0.08% (95% CI: -0.31, 0.15), which was not statistically significant ( $p=0.4874$ ). Changes in FPG from baseline over time were consistent with results for changes in HbA<sub>1c</sub>. The change from baseline FPG values were similar between treatment groups with a non-significant treatment difference (Process 3 - Process 2) of -0.10% (95% CI: -0.74, 0.55),  $p=0.7692$ .

*Dr. Choudhury notes that both processes statistically significantly reduced HBA1C by Week 17. However, the 95% confidence interval (-.31, .15) is slightly out of the non-inferiority margin (-.3, .3). Therefore, the equivalence of the two processes has not been statistically confirmed. Process 3 is marginally numerically superior to Process 2.*

## 7 Review of Safety

### Safety Summary

The primary focus of this safety review relies on data from the 7 integrated phase 3 clinical studies, and 1 additional phase 3 study conducted in renal impairment. Overall baseline characteristics were similar among the primary treatment group comparisons that were evaluated for safety (albiglutide vs. all comparators, and albiglutide vs. placebo).

On-therapy deaths were balanced between albiglutide and all comparators. Overall the frequency of non-fatal SAEs was similar between subjects treated with albiglutide (10.6%) and all comparators (10.3%). The highest numeric imbalance in SAEs not in favor of albiglutide occurred in the system organ class of infections and infestations. Smaller numeric imbalances not in favor of albiglutide were also seen in the cardiovascular and gastrointestinal disorders organ classes. Events of pneumonia, atrial fibrillation, appendicitis occurred more frequently in the albiglutide group. The application was reviewed for the following submission specific safety concerns:

- **Thyroid Tumors:** No trend toward an increased risk of medullary thyroid cancer was identified in this review. However, numerous cases of anatomic thyroid abnormalities were not followed up by biopsy or imaging. Therefore determination of risk and causality is limited by lack of sufficient information.
- **Liver Enzyme Elevations:** A suspected case of drug induced hepatocellular injury was identified meeting criteria for biochemical Hy's law. Cases of hepatocellular injury manifesting in transaminase elevations have been observed with albiglutide treatment in the Phase 3 clinical program. Many cases were confounded with underlying cholestasis. Imbalances in gamma-glutamyl transpeptidase (GGT) elevations were observed to be not in favor of albiglutide when compared to all comparators and placebo treated subjects.
- **Hypoglycemic Events:** A higher incidence of hypoglycemic events occurred in the albiglutide group vs. placebo. Hypoglycemic events were higher when taking background insulin and/or sulfonylurea compared with subjects not taking background insulin and/or sulfonylurea.
- **Gastrointestinal (GI) Events:** Adverse events occurring in >5% of subjects treated with albiglutide with a higher incidence in the albiglutide group compared to placebo were in events of diarrhea and nausea.
- **Immunogenicity:** Approximately 5.5%, 116/2098 subjects treated with albiglutide tested positive for at least 1 post baseline anti-albiglutide antibody (9/116 had preexisting anti-albiglutide antibodies). The proportion of serious adverse events

was generally balanced between antibody positive and negative subjects (12.9 vs. 11.4%, respectively). Injection site reaction (ISR) related discontinuations occurred for 5/45 albiglutide antibody positive subjects. All albiglutide-treated subjects who discontinued treatment for a potential systemic allergic reaction were anti-albiglutide antibody negative.

- **Injection Site Reactions:** A higher proportion of subjects in the albiglutide treatment group experienced an ISR compared with placebo treated subjects and all comparators. More subjects treated with albiglutide withdrew from treatment for injection site reactions (2.1% vs. 0.4%) and injection site rash compared to placebo.
- **Systemic Allergic Reactions (SARs):** Overall SARs in the albiglutide vs. placebo comparison group were balanced (1.8 vs. 1.9%). Subjects receiving albiglutide experienced systemic allergic reaction events of rash, angioedema and possible anaphylaxis.
- **Pancreatic Events:** A higher incidence of acute pancreatitis occurred in albiglutide treated subjects vs. placebo and all comparators. There was 1 fatal case of post endoscopic retrograde cholangiopancreatography (ERCP) necrotizing pancreatitis and 1 case of metastatic pancreatic cancer in the albiglutide treatment arm.
- **Diabetic Retinopathy:** Subjects receiving albiglutide had a higher frequency of diabetic retinopathy events compared to placebo (3.6 % vs. 1.7%, respectively). However funduscopy was not conducted in a rigorous and consistent manner in the clinical program.

**Cardiovascular Events:** A cardiovascular meta-analysis was conducted for the Major Adverse Cardiovascular Events Plus (MACE-plus). This was a composite endpoint consisting of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina. Based on the primary analysis model, the hazard ratio estimate of albiglutide versus comparator is 0.93 with corresponding 97.55% CI (0.55, 1.58). This meets the FDA requirements for filing and approval.

Overall on-therapy adverse events were similar between placebo, albiglutide 30 mg and albiglutide 50 mg (81.2 vs. 84.2 vs. 86.9%, respectively). Up-titration from 30 to 50 mg resulted in a 1 to 2 bpm increase in heart rate.

The percentage of subjects in the albiglutide arm who experienced on-therapy hypoglycemic events was higher in subjects with severe renal impairment (26.3%, n=5) than in subjects with mild (10.9%, n=14) or moderate (9.8%, n=10) renal impairment. In the albiglutide group, on-therapy GI AEs occurred with a higher incidence and higher event rate in subjects with severe renal impairment compared with mild or moderate

renal impairment (mild n=35, moderate n=35, severe n=9). However, due to the small sample size in the severe renal impairment category conclusions are limited

## 7.1 Methods

The safety population includes all randomly assigned subjects who received at least one dose of study treatment. Safety population subjects were analyzed according to the treatment received. Pooled data sets as described in section 7.1.3, were primarily utilized to evaluate the overall safety profile of albiglutide. Deaths, serious adverse events (SAEs), adverse events of special interest, and study discontinuations were reviewed.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical development program investigating albiglutide for T2DM comprises 23 clinical studies: 10 Phase I studies, 5 Phase II studies, and 8 Phase III studies. The primary focus of this safety review is data from the 7 integrated phase 3 clinical studies forming the phase 3 safety population (P3-ISP). Study GLP114130 was conducted in subjects with mild, moderate and severe renal impairment and is reviewed separately for safety in each section.

Figure 2 (Section 5) depicts the trials integrated into the P3-ISP and the clinical pharmacology safety population (CP-ISP). Additional details regarding pooling of clinical studies are provided in section 7.1.3.

Study GHF112670 was conducted in subjects with CHF and was reviewed independently for safety and is discussed in Section 7.7.

### 7.1.2 Categorization of Adverse Events

Adverse events (AEs) were defined as:

- Pre-therapy: Onset date of the AE is before the start date of study medication.
- On-therapy (treatment emergent): Onset date of the AE is on or after the start date of study medication and within 56 days after the last dose.
- Post-therapy: Onset date of the AE is more than 56 days after the last date of study medication.

All adverse events in the integrated datasets were re-coded to MedDRA version 15 by the applicant. Studies that were not integrated were not converted to MedDRA 15. Investigator identified hypoglycemic events are summarized separately. However, serious hypoglycemic events and hypoglycemic events leading to study drug withdrawal

from active treatment were included in appropriate summary sections. AEs are presented in descending order by system organ class (SOC) and by descending order MedDRA preferred term (PT) within each system organ class.

The applicant also identified the following adverse events of special interest (AESI): Hypoglycemic events, systemic allergic reactions, injection site reactions, immunogenicity, liver events, thyroid events, pancreatic events, gastrointestinal events, diabetic retinopathy and cardiovascular events. AESI are discussed separately in this review under section 7.3.5 (Submission Specific Primary Safety Concerns).

### **7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

The primary evaluation of albiglutide's safety profile relies on pooled safety data from 7 phase 3 clinical studies (P3-ISP). This reviewer focused on safety data from pooled comparisons of albiglutide compared to all comparators and placebo.

#### **TREATMENT COMPARISON GROUPINGS**

The applicant utilized the following treatment comparison groupings:

Albiglutide versus All Comparators  
Albiglutide versus Placebo Comparators  
Albiglutide versus Active Comparators

- 2 studies are placebo controlled (GLP112755, GLP112756)
- 3 studies are active controlled (GLP112754, GLP114179, GLP108486)
- 2 studies have both active controls and placebo (GLP112753, GLP112757).

Although there is overlap in subjects in placebo and active comparator groupings, subjects are presented only once in the albiglutide versus all comparators tables. In addition all groupings include continuing background therapy as applicable.

Two studies (GLP112757 and GLP112753) included both active comparator and placebo arms. As such, the albiglutide subjects in these studies are included in the all comparators, the placebo and the active comparators groupings. The albiglutide subjects included in each of the groupings are outlined below:

#### **All Comparator Grouping (N=2116 subjects)**

- 1,193 subjects from studies with only active comparators (GLP114179, GLP108486, GLP112754)

- 573 subjects from studies with both active and placebo comparators (GLP112757, GLP112753)
- 350 subjects from studies with only placebo comparators (GLP112755, GLP112756)

Placebo Grouping (N=923)

- 573 subjects from studies with both active and placebo comparators (GLP112757, GLP112753)
- 350 subjects from studies with only placebo comparators (GLP112755, GLP112756)

Active Comparator Grouping (N=1766)

- 1,193 subjects from studies with only active comparators (GLP114179, GLP108486, GLP112754)
- 573 subjects included both active and placebo comparators (GLP112757, GLP112753)

Table 8 in Section 5.3 provides individual study details for the 8 pivotal trials in the P3 clinical program. Key details of studies in the P3-ISP are briefly delineated below.

- P3-ISP consists of subjects who received at least one dose of study medication in any of the 7 P3 studies (GLP108486, GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, and GLP114179).
- Five of the studies in the P3-ISP were ongoing at the time of the BLA submission (Trials GLP112754, GLP112755, GLP112756, GLP112757 and GLP112753). The integrated analysis includes safety data collected up to the individual study cut off dates after the primary efficacy endpoint, and when all subjects who remained in the respective studies had completed at least 104 weeks of treatment. Four of these studies evaluated the primary efficacy endpoints at 52 weeks and total treatment duration of 3 years (Studies GLP112754, GLP115755, GLP112756, and GLP112757). Study GLP112753 had the primary efficacy endpoint at 104 weeks and total treatment duration of 3 years.
- Study GLP108486 - the primary efficacy endpoint was at 26 weeks and total treatment duration of 52 weeks. Study GLP114179 had planned treatment duration of 32 weeks with the primary efficacy endpoint at the end of treatment. Data from 5 ongoing Phase III studies were integrated together with data from 2 completed Phase III studies.
- Studies GLP108486, GLP112753, GLP112754, GLP112757, and GLP114130 included an option to up-titrate the albiglutide dose to 50 mg weekly if additional

glycemic control was required. Safety data from these studies represents patients treated with albiglutide 30 mg weekly and with albiglutide 50 mg weekly together.

- Study GLP112756- subjects were randomized to either albiglutide 30 mg weekly throughout the active treatment period or albiglutide 30 mg weekly initially followed by forced titration to 50 mg weekly at week 12.
- Study GLP114179- subjects were randomized to a single albiglutide 30 mg weekly treatment arm with forced up-titration to 50 mg weekly at week 6.
- Study GLP112755- subjects were randomized to treatment with albiglutide 30 mg weekly without an option to up titrate.
- Study GLP114130 - the primary efficacy endpoint was at 26 weeks with total treatment duration of 52 weeks. This study was conducted in subjects with mild, moderate, or severe renal impairment, was not integrated in the P3-ISP. Data from this study is presented separately.

#### FOUR MONTH SAFETY UPDATE (4MSU)

The four month safety update (4MSU) included pooled data from the 5 ongoing Phase 3 studies (GLP112753, GLP112754, GLP115755, GLP112756, and GLP112757) from the time of the 2 year data cutoff for the BLA submission up to the data cutoff date of December 24, 2012. The update provided integrated safety data from 5 ongoing P3 studies (Trials GLP112754, GLP115755, GLP112756, GLP112757 and GLP112753). The primary comparison grouping in the 4MSU was albiglutide compared to all comparators.

#### CUMULATIVE DATA

Cumulative data was presented with the 4MSU submission from all 7 integrated P3 studies (P3-ISP), through December 14, 2012. Data was presented for Deaths, SAEs and adverse events of special interest.

#### PROCESS 2 to PROCESS 3 ALBIGLUTIDE DRUG PRODUCT

The applicant did not make a distinction in the safety review between Process 2 and Process 3 albiglutide as the bioequivalence and clinical comparability of Process 2 and Process 3 albiglutide was demonstrated in Study GLP114856. In the Phase 3 program a Process 2 to Process 3 switch strategy was employed for studies GLP112756 and GLP112754. Process 2 albiglutide was switched out for Process 3 albiglutide in a

double-blinded manner following the time point of the primary efficacy and safety assessments in both studies.

## CLINICAL PHARMACOLOGY STUDIES (CP- ISP or P1-ISP)

Subjects treated with study medication in the following 10 clinical pharmacology studies (GLP105229, GLP106073, GLP107030, GLP107032, GLP107085, GLP107724, GLP107865 [Phase IIa-Cohorts C and D], GLP108366, GLP111680, and GLP111681) are included in the Clinical Pharmacology Integrated Safety Population (CP-ISP). Five clinical pharmacology Phase II studies (GLP114856, GLP110125, GLP110932, GHF112670, and GLP108372) and one Phase I study (GLP108370) were not integrated. In addition, two cohorts in Study GLP107085 were not integrated (Cohort A and Cohort B: 15 mg and 30 mg x 4 doses, respectively).

Phase IIa study GHF112670 was conducted in heart failure and the final study report was submitted with the 4MSU.

## 7.2 Adequacy of Safety Assessments

Safety and tolerability assessments included all adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (e.g., cardiovascular, pancreatitis, thyroid tumors, systemic allergic reactions, immunogenicity, injection site reaction, liver events, hypoglycemia, gastrointestinal events and diabetic retinopathy. Laboratory parameters, blood pressure, heart rate, and ECG parameters were also followed throughout the clinical program.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

#### Demographics

#### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

As depicted in Table 25, overall baseline characteristics were similar among the treatment groupings. As noted previously, 2 studies have both active controls and placebo treated subjects (GLP112753, GLP112757). Although there is overlap in subjects in placebo and active comparator groupings, subjects are presented only once in the albiglutide versus all comparators tables.

Across all treatment groupings the mean age was 54 to 55 years. BMI was balanced between treatment arms and approximately 30% of subjects enrolled in the program had diabetes  $\geq 10$  years. Mean HbA1c ranged from 8.13 to 8.25. Approximately 43.4 - 51.2% of subjects had HbA1c  $< 8\%$ ; 27.2 - 33.2% had HbA1c  $\geq 8\%$  to 9%, and 21.6 to

23.8% had HbA1c  $\geq 9\%$ . There was a higher proportion of women in the albiglutide arm compared to placebo (49% vs. 43%, respectively).

#### RENAL STUDY (GLP114130)

Demographics were similar across the renal study as depicted in Table 26. A greater proportion of subjects in the albiglutide group had a baseline HbA1c value of less than 8.0% compared with subjects in the sitagliptin group.

**Table 25: Demographics and Baseline Characteristics by Treatment Group Comparisons (P3-ISP)**

	Albiglutide vs. All Comparators		Albiglutide vs. Placebo		Albiglutide vs. Active Comparators	
	All Comparators (N=2284)	Albiglutide (N=2116)	Placebo (N=468)	Albiglutide (N=923)	Active Comparators (N=1816)	Albiglutide (N=1766)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Mean Age at Randomization (years) (SD)	55.2 (9.77)	54.9 (9.86)	54.9 (10.13)	54.2 (10.20)	55.3 (9.68)	55.1 (9.64)
Mean Baseline HbA1c (%) (SD)	8.21 (0.877)	8.22 (0.902)	8.14 (0.905)	8.13 (0.880)	8.22 (0.869)	8.25 (0.897)
<b>Body Mass Index (BMI) (kg/m<sup>2</sup>)</b>						
Mean (SD)	32.74 (5.602)	33.02 (5.705)	33.19 (5.460)	32.97 (5.576)	32.63 (5.634)	32.89 (5.725)
<b>Age Category, n (%)</b>						
<65 years	1899 (83.1)	1780 (84.1)	390 (83.3)	772 (83.6)	1509 (83.1)	1488 (84.3)
≥65 to <75 years	351 (15.4)	305 (14.4)	70 (15.0)	139 (15.1)	281 (15.5)	255 (14.4)
≥75 years	34 (1.5)	31 (1.5)	8 (1.7)	12 (1.3)	26 (1.4)	23 (1.3)
<b>Sex</b>						
Female	1087 (47.6)	1037 (49.0)	202 (43.2)	453 (49.1)	885 (48.7)	887 (50.2)
Male	1197 (52.4)	1079 (51.0)	266 (56.8)	470 (50.9)	931 (51.3)	879 (49.8)
<b>Duration of Diabetes Category</b>						
<5 years	859 (37.6)	761 (36.0)	206 (44.0)	410 (44.4)	653 (36.0)	575 (32.6)
≥5 to <10 years	746 (32.7)	692 (32.7)	150 (32.1)	310 (33.6)	596 (32.8)	591 (33.5)
≥10 years	679 (29.7)	663 (31.3)	112 (23.9)	203 (22.0)	567 (31.2)	600 (34.0)
<b>Baseline HbA1c Category</b>						
<8.0%	1018 (44.6)	960 (45.4)	230 (49.1)	473 (51.2)	788 (43.4)	774 (43.8)
≥8 to <9%	740 (32.4)	651 (30.8)	137 (29.3)	251 (27.2)	603 (33.2)	572 (32.4)
≥9%	526 (23.0)	505 (23.9)	101 (21.6)	199 (21.6)	425 (23.4)	420 (23.8)
<b>Race/Ethnicity</b>						
Non-Hispanic African American	274 (12.0)	322 (15.2)	61 (13.0)	120 (13.0)	213 (11.7)	280 (15.9)
Non-Hispanic White	1085 (47.5)	1018 (48.1)	231 (49.4)	442 (47.9)	854 (47.0)	826 (46.8)
Hispanic	660 (28.9)	544 (25.7)	133 (28.4)	275 (29.8)	527 (29.0)	450 (25.5)
Asian	220 (9.6)	180 (8.5)	31 (6.6)	61 (6.6)	189 (10.4)	173 (9.8)
Other	45 (2.0)	52 (2.5)	12 (2.6)	25 (2.7)	33 (1.8)	37 (2.1)
<b>Renal Impairment (MDRD)<sup>1</sup></b>						
Normal (eGFR≥90 mL/min/1.73m <sup>2</sup> )	902 (39.5)	804 (38.0)	149 (31.8)	298 (32.3)	753 (41.5)	698 (39.5)
Mild (60 ≤eGFR <90 mL/min/1.73m <sup>2</sup> )	1207 (52.8)	1139 (53.8)	274 (58.5)	548 (59.4)	933 (51.4)	922 (52.2)

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Moderate (30 $\geq$ eGFR <60 mL/min/1.73m <sup>2</sup> )	174 (7.6)	173 (8.2)	45 (9.6)	77 (8.3)	129 (7.1)	146 (8.3)
Severe (eGFR <30 mL/min/1.73m <sup>2</sup> )	1 (0.0)	0	0	0	1 (0.1)	0

Source SCS – Modified from Table 12, Page 51-53. Although there is overlap in subjects in placebo and active comparator groupings, subjects are presented only once in the albiglutide versus all comparators tables. Phase III Integrated Safety Database (Studies GLP108486, GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, and GLP114179); final data through and partial data after Week 104.

1. Baseline renal impairment as determined using the Modification of Diet in Renal Disease Study Group (MDRD) formula for the eGFR = estimated glomerular filtration rate, SD = standard deviation.

**Table 26: Demographics and Baseline Characteristics by Treatment Group Comparisons and degree of renal impairment (Renal Study GLP114130)**

	Albiglutide				Sitagliptin			
	Mild (N=128)	Moderate (N=102)	Severe (N=19)	Total (N=249)	Mild (N=128)	Moderate (N=101)	Severe (N=17)	Total (N=246)
<b>Age at randomization (years)</b>								
Mean (SD)	61.9 (7.82)	65.3 (8.67)	60.4 (8.21)	63.2 (8.37)	61.8 (8.83)	65.2 (9.02)	65.5	63.5 (9.02)
<b>Age category, n (%)</b>								
<65 years	79 (61.7)	49 (48.0)	13 (68.4)	141 (56.6)	79 (61.7)	49 (48.5)	10 (58.8)	138 (56.1)
≥65 years	49 (38.3)	53 (52.0)	6 (31.6)	108 (43.4)	49 (38.3)	52 (51.5)	7 (41.2)	108 (43.9)
<b>Sex, n (%)</b>								
Female	61 (47.7)	42 (41.2)	10 (52.6)	113 (45.4)	55 (43.0)	48 (47.5)	13 (76.5)	116 (47.2)
Male	67 (52.3)	60 (58.8)	9 (47.4)	136 (54.6)	73 (57.0)	53 (52.5)	4 (23.5)	130 (52.8)
<b>Duration of diabetes (years)<sup>2</sup></b>								
Mean (SD)	9.41 (6.834)	11.70 (7.502)	15.77 (8.074)	10.83 (7.403)	10.01 (7.141)	13.53 (9.076)	12.49 (11.660)	11.62 (8.476)
<b>Duration Category, n (%)</b>								
<7 years	57 (44.5)	36 (35.3)	6 (31.6)	99 (39.8)	56 (43.8)	25 (24.8)	7 (41.2)	88 (35.8)
≥7 to ≥13 years	45 (35.2)	29 (28.4)	1 (5.3)	75 (30.1)	35 (27.3)	34 (33.7)	4 (23.5)	73 (29.7)
>13 years	26 (20.3)	37 (36.3)	12 (63.2)	75 (30.1)	27 (28.9)	42 (41.6)	6 (35.3)	85 (34.6)
<b>Baseline HbA1c (%)</b>								
Mean (SD)	8.03 (1.147)	8.26 (0.924)	8.05 (0.746)	8.13 (1.036)	8.16 (0.896)	8.26 (0.945)	8.60 (1.196)	8.23 (0.942)
<8.0%	77 (60.2)	45 (44.1)	9 (47.4)	131 (52.6)	57 (44.5)	44 (43.6)	6 (35.3)	107 (43.5)
≥8.0%	51 (39.8)	57 (55.9)	10 (52.6)	118 (47.4)	71 (55.5)	57 (56.4)	11 (64.7)	139 (56.5)
<b>Severity of renal impairment, n (%)</b>								
Mild				128 (51.4)				128 (52.0)
Moderate				102 (41.0)				101 (41.1)
Severe				19 (7.6)				17 (6.9)

Modified from CSR GLP114130 Table 7 & Table 8, Page 81-84.

## **Exposure**

### **PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)**

At the time of the BLA submission the clinical trials safety database for albiglutide included 6258 subjects (Phase I/II/III), including 5811 subjects with T2DM. Of the 5811 T2DM subjects, approximately 3122 have been administered at least one dose of albiglutide.

Overall in the P3-ISP exposure was similar between albiglutide and all comparators and active comparators as depicted in Table 27. In the 4 trials with placebo-control arms randomization was 2:1 (albiglutide: placebo). Total placebo exposure was 841 person-years in the placebo treated subjects and 1794 person years in albiglutide treated patients. Across all comparison groups 37.3% to 58.9% of subjects had exposure of >104 -156 weeks duration.

### **Exposure based on Dose**

#### **PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)**

Table 28 details exposure based on dose. Exposure for the 30 mg dose was 1720 person-years for 2116 subjects. Of these subjects, 1416 were exposed to the 50 mg dose (optional and forced up-titration) for a total exposure of 1650 person-years to the 50 mg albiglutide dose. The applicant notes that 700 subjects had a maximum dose of 30 mg with a total exposure of 1090 person-years. For subjects who optionally up titrated the mean time to up-titration was 31 weeks.

#### **RENAL STUDY (GLP114130)**

Exposure was similar between the albiglutide and sitagliptin group (253.84 vs. 238.26 total person years). See Table 29.

#### **FOUR MONTH SAFETY UPDATE (4MSU)**

At the 4 month safety update total person-years of exposure since the individual study data cutoffs used for the original BLA submission were 830.64 years (albiglutide treatment arm) and 935.52 years (all comparators arm).

**Table 27: P3-ISP Treatment Exposure by Treatment Group Comparisons**

	Albiglutide vs. All Comparators		Albiglutide vs. Placebo		Albiglutide vs. Active	
	All Comparators (N=2284)	Albiglutide (N=2116)	Placebo (N=468)	Albiglutide (N=923)	Active Comparators (N=1816)	Albiglutide (N=1766)
N	2284	21	468	923	18	1766
Mean (SD)	74.9 (43.12)	75.1 (43.41)	85.7 (42.79)	93.4 (39.21)	72.1 (42.78)	70.5 (42.66)
<b>Number (%) of Subjects with Exposure of:</b>						
1 day to ≤12 weeks	179 (7.8)	134 (6.3)	39 (8.3)	61 (6.6)	140 (7.7)	115 (6.5)
>12 weeks to ≤26 weeks	124 (5.4)	123 (5.8)	48 (10.3)	47 (5.1)	76	109 (6.2)
>26 weeks to ≤52 weeks	615 (26.9)	677 (32.0)	33 (7.1)	64 (6.9)	582 (32.0)	652 (36.9)
>52 to ≤104 weeks	438 (19.2)	297 (14.0)	107 (22.9)	207 (22.4)	331 (18.2)	231 (13.1)
>104 to ≤156 weeks	928 (40.6)	885 (41.8)	241 (51.5)	544 (58.9)	687 (37.8)	659 (37.3)
>156 weeks	0	0	0	0	0	0
<b>Total Person-years<sup>2</sup></b>	3628.46	3369.65	840.73	1794.28	2787.	2655.30
Total person-years through week 26 <sup>3</sup>	1345.86	1256.10	273.00	547.65	1072.	1046.06
Total person-years through week 52 <sup>3</sup>	2179.84	2026.95	456.06	941.08	1723.	1665.17
Total person-years post week 52 <sup>4</sup>	1448.62	1342.70	384.67	853.20	1063.	990.13

Modified from SCS Table7, Page 40.

1. Duration of exposure (weeks) = (date of last dose – date of first dose + 1)/7.
2. Total person-years are equal to the sum of (last dose date – first dose date + 57)/365.25 for all subjects in the Phase III integrated safety population.
3. The total person-years through a specific time period is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the treatment period being summarized.
4. Derived by subtracting the week 52 exposure from the overall exposure

**Table 28: P3-ISP Treatment Exposure to Albiglutide by Actual Dose Level**

	Albiglutide 30 mg (N=2116)	Albiglutide 50 mg Optional Titration	Albiglutide 50 mg Forced Titration	Albiglutide 50 mg Total (N=1416)
<b>Duration of Exposure (weeks)<sup>1</sup></b>				
N	2116	940	476	1
Mean (SD)	39.8 (39.91)	61.6 (34.50)	35.3 (31.46)	52.8 (35.73)
<b>Number (%) of Subjects with Exposure of:</b>				
1 day to ≤12 weeks	595 (28.1)	79 (8.4)	30	109
>12 weeks to ≤26 weeks	595 (28.1)	95 (10.1)	360 (75.6)	455 (32.1)
>26 weeks to ≤52 weeks	405 (19.1)	243 (25.9)	19	262 (18.5)
>52 to ≤104 weeks	190 (9.0)	426 (45.3)	18	444 (31.4)
>104 to ≤156 weeks	331 (15.6)	92 (9.8)	49	141 (10.0)
>156 weeks	0	0	0	0
<b>Total Person-years<sup>2</sup></b>	1719.96	1254.38	395.31	1649
Total person-years through week 26 <sup>3</sup>	881.66	157.02	217.42	374
Total person-years through week 52 <sup>3</sup>	1205.12	520.93	300.90	821

Source Data: [SCS Table 8, Page 42](#). SD, standard deviation. Note: In this summary a subject's exposure is summarized according to the actual time at a given dose level. Studies GLP108486, GLP112753, GLP112754, and GLP112757 have optional up-titration of albiglutide from 30 mg to 50 mg as needed. Study GLP112756 has forced titration of albiglutide from 30 mg to 50 mg at Week 12 for one treatment group. Study GLP114179 has forced titration of albiglutide from 30 mg to 50 mg at Week 6 for the albiglutide group.

1. Duration of exposure (weeks) = (date of last dose – date of first dose + 1)/7.

2. Total person-years are equal to the sum of (last dose date – first dose date + 57)/365.25 for all subjects in the Phase III integrated safety population.

3. The total person-years through a specific time period is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the treatment period being summarized.

Table 29: Renal Study (GLP114130) – Exposure Overall Treatment

	<b>Albiglutide (N=249) n (%)</b>	<b>Sitagliptin (N=246) n (%)</b>
Duration of exposure <sup>1</sup> (days)		
N	249	246
Mean (SD)	316.3 (96.30)	297.9 (112.64)
Median	358.0	358.0
Minimum, maximum	1,	1,
Total person-years <sup>2</sup>	253.8	238.3

Source CSR GLP114130 Table 11, Page 90.

1. Duration of exposure (days) = date of last dose – date of first dose +1.

2. Total person-years = sum of (date of last dose – date of first dose + 57)/365.25 for all subjects

## 7.2.2 Explorations for Dose Response

- Studies GLP108486, GLP112753, GLP112754, GLP112757, GLP114130) included an option to up-titrate the albiglutide dose to 50 mg weekly if additional glycemic control was required. Safety data from these studies represents patients treated with albiglutide 30 mg weekly and with albiglutide 50 mg weekly together.
- Study GLP112756 included subjects randomized to either albiglutide 30 mg weekly throughout the active treatment period or albiglutide 30 mg weekly initially followed by forced titration to 50 mg weekly at week 12.
- Study GLP114179 included subjects randomized to a single albiglutide 30 mg weekly treatment arm with forced up-titration to 50 mg weekly at week 6.
- In study GLP112755 subjects were randomized to treatment with albiglutide 30 mg weekly with no up-titration.

## 7.2.3 Special Animal and/or In Vitro Testing

Please refer to Dr. Ronald Wange's review for details

## 7.2.4 Routine Clinical Testing

Hematology parameters: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils, platelets, erythrocyte, segmented neutrophils, and leukocyte count.

Serum chemistry parameters: lipids, albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), bicarbonate (carbon dioxide content), blood urea nitrogen (BUN), calcitonin, calcium, chloride, serum creatinine, direct bilirubin, gamma-glutamyl transferase (GGT), glucose, lipase, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, uric acid, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and free fatty acids.

### Studies with primary endpoint at 52 weeks and 2 year extension

Hematology and chemistry assessments were performed at visits (V), V1 (Screening), V5 (Week-1), V6 (Baseline), V7 through V25 (Weeks 1 to 156), and V26 (Week 164, Follow-up).

All 12-lead electrocardiograms (ECGs) were conducted at V1 (Screening), V6 (Baseline), V11 (Week 12), V17 (Week 52), V21 (Week 104), and the end-of treatment

visit (Week 156). EKGs were performed in triplicate (approximately 5 minutes apart) and over read by a central reader.

A complete physical examination was performed at V1 (Screening), V17 (Week 52), V21 (Week 104), and the end-of-treatment visit (Week 156). Assessment of vital signs (blood pressure and pulse rate) occurred at every visit.

A standard urinalysis was obtained at V1 (Screening), V14 (Week 24), V17 (Week 52), V21 (Week 104), and end of Treatment). Urine samples for assessment of microalbuminuria from the urine-creatinine ratio were collected at V1 (Screening), V6 (Baseline), V17 (Week 52), V21 (Week 104), and V25 (end of treatment).

Time and events tables for studies with primary endpoints that were not at 52 weeks are provided in individual trial protocols for studies GLP108486 (Table 3 page 47), GLP114130 (Table 2, page 47) GLP114179 (Table 2, page 42) and GLP112753 (Table 2, page 44).

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

Please see Dr. Ritesh Jain and Dr. Anshu Mather's review for details

### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

Important safety issues with consideration to related GLP-1 mimetic (US approved liraglutide, exenatide, and exenatide extended release) include; acute pancreatitis, gastrointestinal side effects, hypoglycemia, especially when used in combination with a sulfonylurea, hypersensitivity reactions as a result of anti-drug antibodies, and thyroid C-cell tumors in rats.

## **7.3 Major Safety Results**

### **7.3.1 Deaths**

At the time of the original BLA submission overall death rates were comparable between albiglutide and all comparators (0.8% in both arms) with the highest incidence of deaths in the albiglutide group occurring in the cardiovascular disorders SOC. Most deaths were due to single event preferred terms except for events myocardial infarctions which occurred in 0.1% (3/2116) of albiglutide titrated subjects vs. 1 subject in the all comparators arm.

Cumulative data (including the 4 month safety update) demonstrated that the overall incidence of deaths remained balanced between the albiglutide and all comparators

treatment arms (0.9%, 20/2116 and 1%, 22/2284, respectively). The highest proportion of deaths for both the albiglutide and all comparators treatment groups occurred in the neoplasms SOC (0.3%, albiglutide vs. 0.4% in all comparators). The majority of neoplasm related deaths in both arms were single preferred term events. The exception was for events of lung cancer. In the albiglutide arm there were 2 (0.1%) on-therapy events of lung metastatic adenocarcinoma. In all comparators there were 4 on-therapy lung cancer related deaths for the following preferred terms; (2 (0.1%) subjects with events of malignant lung neoplasms, 1 subject had metastatic lung cancer and 1 subject developed non-small cell lung cancer. Deaths were reported more frequently in men than in women in the albiglutide group. Overall, there did not appear to be a consistent pattern relative to all comparators.

### PHASE 2 SAFETY POPULATION

There were no deaths in the clinical pharmacology integrated studies.

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

At the time of the BLA submission 38 subjects had a fatal SAE in the P3-ISP.

- 34 subjects had an on-therapy fatal SAEs (16 albiglutide treated vs.18 all comparators)
- 4 subjects had post therapy fatal SAEs (3 albiglutide group (one of these subjects originally classified as post-therapy and later classified as on-therapy) vs. 1 in all comparator).

As detailed in Table 30, the highest proportion of deaths at the time of the BLA submission occurred in the cardiovascular and neoplasm disorders SOCs for both treatment groups. The overall incidence (0.8% in both groups) and event densities for deaths were similar between both treatment arms (0.47 events per 100 person-years in the albiglutide group and 0.50 events per 100 person-years in all comparators group).

**Table 30: P3-ISP- On-therapy Fatal Serious Adverse Events Albiglutide vs. All Comparators**

SOC Preferred Term	All Comparators (N=2284)	Albiglutide (N=2116)
	n (%)	n (%)
Any Event	18 (0.8)	16 (0.8)
<b>Cardiac disorders</b>		
Any Event	4 (0.2)	6 (0.3)
Acute myocardial infarction	1 (0.0)	3 (0.1)
Cardio-respiratory arrest	1 (0.0)	1 (0.0)
Cardiovascular disorder	0	1 (0.0)
Myocardial infarction	0	1 (0.0)

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Cardiomyopathy	1 (0.0)	0
Coronary artery insufficiency	1 (0.0)	0
<b>Neoplasms<sup>1</sup></b>		
Any Event	8 (0.4)	4 (0.2)
B-cell lymphoma	1 (0.0)	1 (0.0)
Lung adenocarcinoma metastatic	0	1 (0.0)
Esophageal carcinoma	0	1 (0.0)
Pancreatic carcinoma metastatic	0	1 (0.0)
Acute myeloid leukemia	1 (0.0)	0
Adenocarcinoma pancreas	1 (0.0)	0
Hepatic cancer metastatic	1 (0.0)	0
Lung cancer metastatic	1 (0.0)	0
Lung neoplasm malignant	1 (0.0)	0
Metastases to liver	1 (0.0)	0
Non-small cell lung cancer	1 (0.0)	0
<b>General disorders and administration site conditions</b>		
Any Event	3 (0.1)	2 (0.1)
Drowning	0	1 (0.0)
Sudden death	1 (0.0)	1 (0.0)
Death	1 (0.0)	0
Sudden cardiac death	1 (0.0)	0
Vascular disorders		
Any Event	1 (0.0)	2 (0.1)
Arteriosclerosis	1 (0.0)	1 (0.0)
Hemorrhage	0	1 (0.0)
<b>Blood and lymphatic system disorders</b>		
Any Event	0	1 (0.0)
Anemia	0	1 (0.0)
Psychiatric disorders		
Any Event	0	1 (0.0)
Completed suicide	0	1 (0.0)
<b>Infections and infestations</b>		
Any Event	2 (0.1)	0
Meningitis pneumococcal	1 (0.0)	0
Septic shock	1 (0.0)	0

Source: ISS Table 78, Page 244. Note: On-therapy AEs – events with a start date on or after the first day of study medication and within 56 days after the end of study medication. For each level of summarization, a subject is counted once if the subject reported one or more events. Percentages are based on the number of subjects in each treatment grouping. 1.-Neoplasms= benign, malignant and unspecified (incl. cysts and polyps).

Individual subject descriptions of deaths during the on-therapy period are summarized in Table 31.

**Table 31: P3-ISP: On-therapy Fatal Serious Adverse Events by Subjects**

Study #	Subject ID	Age (yr.)/ Sex/Race <sup>1</sup>	Fatal Serious Adverse Event Preferred Term	Time Since First Dose/Time Since Last Dose
<b>Albiglutide</b>				
GLP1108486	1127486001	55/Male/White	Completed suicide	33 / 3
GLP1108486	8410486006	61/Male/Asian	Acute myocardial infarction	84 / 7
GLP112753	3508753988	56/Female/White	Cardio-respiratory Arrest	281 / 1
GLP112754	3569754982	69/Male/White	Hemorrhage	807 / 3
GLP112754	3793754987	61/Male/Hispanic	Esophageal carcinoma	140/69 <sup>3</sup>
GLP112754	7060754980	65/Male/White	Cardiovascular Disorder	827 / 4
GLP112754	7062754999	66/Male/White	Acute myocardial infarction	58 / 2
GLP112754	7065754931	59/Male/AfrAm	Anemia	148 / 8
GLP112755	7062755986	60/Male/White	Acute myocardial infarction	448 / 7
GLP112756	3405756987	57/Male/White	Drowning	32 / 4
GLP112756	3508756987	65/Female/White	B-cell lymphoma	180 / 1
GLP112756	3614756987	62/Male/White	Pancreatic carcinoma metastatic	694 / 1
GLP112756	3696756987	72/Female/White	Lung adenocarcinoma metastatic	319 / 4
GLP112757	3474757986	62/Female/White	Sudden death	501 / 41
GLP114179	1002179019	58/Female/White	Arteriosclerosis	40 / 4
GLP114179	3308179024	54/Male/Hispanic	Myocardial infarction	40 / 5
<b>Placebo</b>				
GLP112753	3435753999	55/Male/AfrAm	Cardio-respiratory Arrest	154 / 21
GLP112755	3433755980	61/Male/White	Non-small cell lung Cancer	19 / 5
GLP112755	3616755986	48/Male/Hispanic	Metastases to liver	217 / 51
GLP112755	3704755986	54/Male/AfrAm	Cardiomyopathy	118 / 5
GLP112757	3624757988	51/Female/AfrAm	Meningitis pneumococcal	196 / 29
<b>Pre-prandial Lispro</b>				
GLP108486	3101486006	76/Female/Hispanic	Acute myeloid leukemia	219 / NR
<b>Glimepiride</b>				

GLP112753	3473753988	60/Female/White	B-cell lymphoma	652 / 18
GLP112753	3543753990	61/Male/ White	Hepatic cancer Metastatic	455 / 0
GLP112753	3648753988	69/Male/AfrAm	Lung cancer metastatic	141 / 5
<b>Sitagliptin</b>				
GLP112753	5471753996	44/Male/Hispanic	Acute myocardial infarction	459 / 4
<b>Insulin glargine</b>				
GLP112754	7060754986	56/Male/White	Sudden cardiac death	349 /NR
GLP112754	7063754908	72/Male/AfrAm	Death (PT: death, natural causes)	298 /NR
GLP112754	7665754907	48/Male/White	Coronary artery insufficiency	203 /NR
<b>Pioglitazone</b>				
GLP112757	3486757987	62/Male/White	Septic shock	290 / 3
GLP112757	3525757986	71/Male/White	Lung neoplasm malignant	82 / 5
GLP112757	3873757986	58/Male/Hispanic	Adenocarcinoma pancreas	17 / 3
<b>Liraglutide</b>				
GLP114179	1368179007	56/Male/White	Arteriosclerosis	23 /NR
GLP114179	3309179023	64/Male/Hispanic	Sudden death	207 /NR

Source Data: ISS Table 79, Page 246 – 247. SAE = serious adverse event; PT = preferred term. Note: Data cutoff: 31 January 2012.

1. Race/ethnicity: AfrAM = Non-Hispanic African American, White = Non-Hispanic white.

2. For active comparator subjects from the open-label studies (GLP108486, GLP112754 and GLP114179), time since last dose is not applicable due to daily injections.

## Death Narratives

### On-therapy Albiglutide Death Narratives (P3-ISP)

Narratives for on-therapy fatalities in the albiglutide group are briefly described below.

Subject 1127486001: 55-year old male with a past medical history of manic depressive disorder, anxiety and attention deficit disorder committed **suicide** with a gunshot wound on study day 33.

**Reviewer Comment:** *Although the event occurred shortly after initiation of study drug, the subject's underlying psychiatric history confounds an assessment of study drug causality.*

Subject 3508753988: 56-year old female with a medical history of ischemic heart disease experienced **cardio-respiratory arrest** on study day 281.

**Reviewer Comment: One month prior to death the subject underwent an open reduction internal fixation for an ankle fracture. Since an autopsy was not performed the exact cause of death is unknown.**

Subject 3569754982: 70-year old male with a medical history of chronic obstructive pulmonary disease, ischemic heart disease, hypertension, congestive heart failure, dyslipidemia, smoking, myocardial infarction, and history of transient ischemic attack experienced new onset atrial fibrillation on study day 196. The subject underwent successful cardioversion and did not require drug therapy for management of atrial fibrillation. He received aspirin for coronary artery disease. On study day 341 he experienced severe bradycardia secondary to first degree AV block and had a pacemaker placed. Approximately 807 days after the first dose of albiglutide the subject experienced intracerebral **hemorrhage** and cerebral infarct that resulted in death. Blood pressure upon presentation to the emergency department was elevated at 225/131 mmHg. An autopsy was not performed.

**Reviewer Comment: The etiology of the death event in this case is confounded by underlying risk factors for stroke development which include cardiovascular disease, hypertension, dyslipidemia, atrial fibrillation and an elevation in blood pressure at the time of presentation.**

Subject 3793754987: 61-year old male with a history gastroesophageal reflux disease and a lung mass (unknown etiology) was diagnosed with **esophageal carcinoma** 140 days after the first dose of albiglutide. The subject did not report the event of esophageal carcinoma to the study investigator and withdrew from the study on day 135 and was lost to follow-up. He died approximately 200 days after the first dose of albiglutide. Additional information was not provided.

**Reviewer Comment: Clinical details to establish the exact cause of death are lacking since the subject was lost to follow-up. In addition the narrative lacked relevant information regarding the etiology of the prior lung mass and risk factors for the development of esophageal cancer (smoking, tobacco chewing, alcohol use, and presence of achalasia or Barrett's esophagus).**

Subject 7060754980: 67-year old male with a history of gastroesophageal reflux disease and cholelithiasis developed sudden hemoptysis and ventricular fibrillation resulting in death on study day 827. An autopsy was not performed and the preferred term for the cause of death was **cardiovascular disorder**. Per the narrative the subjects likely experienced sudden cardiovascular death. Additional details were not provided.

**Reviewer Comment: Clinical details to establish the exact cause of death were insufficient to make a determination of causality.**

Subject 7065754931: 59-year old male with a history hypertension and dyslipidemia developed atrial fibrillation during the run in placebo period. On study day 148 he was hospitalized for melena and dizziness and was assessed to have **anemia** secondary to gastrointestinal bleeding secondary to questionable over-warfarinization [(INR 4.72 and hemoglobin 5.1 g/l (local lab, reference ranges not provided)]. The subject received normal saline intravenous fluids and a blood transfusion of three units for treatment for this event. Although a gastroscopy was planned it was not performed since the subject died one day after hospitalization. An autopsy was not performed and the death certificate was not provided at the time of the narrative.

***Reviewer Comment: The SAE preferred term for this fatal case was “anemia.” The attributed cause of death appears incorrect as review of the narrative suggests that the anemia may have resulted from a possible gastrointestinal bleed secondary to aspirin and warfarin use. An information request for clarification of the event term “anemia” was sent to the applicant. The applicant responded that “the admitting physician speculated that a GI bleed was the etiology, possibly due to ‘over-warfarinization’. It was reported that no autopsy was performed. The Clinical Endpoint Committee adjudicated the case as a GI etiology for the death. The etiology on the death certificate was “anemia”, and although queried on the cause of death by the sponsor, it was not changed by the investigator.”***

Subject 7062755986: 61-year old male with a history of ischemic heart disease, hypertension, and myocardial infarction experienced a fatal **acute myocardial infarction** 448 days after the first dose of investigational product. Two months prior to death a supraventricular rhythm, atrial premature contractions and atrial bigeminy were noted by the investigator on routine screening ECG. However, the ECG findings were not considered to be clinically significant by the investigator due to the subject’s medical history.

Subject 3405756987: 57-year old died during a kayaking accident on study day 32. He was overturned and trapped under a log jam resulting in **drowning**.

Subject 3508756987: 65-year old female with a past medical history of hypertension, dyslipidemia, and ischemic heart disease developed malignant diffuse large **B-cell type lymphoma** 180 days after the first dose of investigational product. She underwent three stem cell transplants and received chemotherapy. The investigational product was withdrawn on day 517 after a third stem cell transplant. The subject died on day 582 of unknown complications of the lymphoma.

***Reviewer Comment: A follow up information request clarified a positive past history of tobacco use. The subject did not have a history of prior malignancy, organ transplantation or autoimmune diseases, specific information regarding***

***past radiation or chemotherapy treatment was not reported. The applicant noted that information regarding occupational exposures or family history was not specifically collected. Although a relationship between study drug and the development of lymphoma 180 days after the first dose cannot be excluded, the case lacks relevant information to determine causality.***

***Overall, deaths due to B cell lymphoma were balanced between albiglutide and all comparators. However the one fatal event of B cell lymphoma occurred in a subject randomized to glimepiride on study day 652.***

Subject 3614756987: 65-year old male with a medical history of hypertension, dyslipidemia, impotence and unstable angina was diagnosed with metastatic pancreatic carcinoma on study day 694, following a 3-week history of moderate abdominal pain, weight loss and cachexia. The applicant worked as a furniture refinisher and the narrative notes possible hepatitis B or C exposure with prior blood transfusion. The subject's father died of liver cancer. Endoscopic ultrasound guided aspirate (neck of pancreas mass) showed malignant cell clusters. Computed tomography angiogram showed bilateral lower lobe pulmonary emboli and moderate diffuse ascites and several masses in the liver and nodular infiltration of the omentum and mesentery. The investigational product was withdrawn due to the event of **pancreatic carcinoma** on day 722 and the subject died 16 days after the last dose and 738 days after the start of study medication. The investigator considered there was a reasonable possibility that the event of pancreatic carcinoma metastatic may have been caused by the investigational product.

***Reviewer Comment: Although a relationship between the development of pancreatic cancer and study drug cannot be excluded the case is confounded by the subject's older age, male gender, obesity (BMI 31 kg/m<sup>2</sup>), history of type 2 diabetes, and tobacco use. Follow-up information confirmed that the subject reported that he did not consume alcohol.***

***Overall, deaths due to pancreatic carcinoma were balanced between treatment arms with one event occurring in a subject randomized to pioglitazone.***

***Subject 3873757986: 58 year old male with a history of Hepatitis A randomized to pioglitazone was found to have pancreatic adenocarcinoma on study day 17. However, the event of pancreatic cancer development within 3 weeks of study drug administration is not likely related to investigational product.***

Subject 3696756987: 73-year old female with a history of unknown pulmonary nodule, bilateral breast cancer, and cervical carcinoma was found to have **metastatic lung adenocarcinoma** on day 319. The subject died on study day 380.

***Reviewer Comment: The presence of a baseline pulmonary nodule and history of prior malignancies confounds determination of a relationship to study drug. In***

***addition the subject's smoking history and family history of lung cancer was not provided.***

Subject 3474757986: 62-year old female with a medical history of hypertension and dyslipidemia experienced **sudden death** 501 days after the first dose of investigational product and 41 days after study medication was discontinued. An autopsy report or death certificate was not available.

Subject 1002179019: 58-year old female with a history of hypertension, dyslipidemia, and hypertensive atherosclerotic cardiovascular disease was found dead at home 40 days after the first dose of albiglutide. Autopsy noted the cause of death as coronary artery **atherosclerosis** due to hypertensive atherosclerotic cardiovascular disease with diabetes mellitus listed as a significant condition.

Subject 3308179024: 54-year old male with a past medical history of obesity, hypertension and dyslipidemia experienced a fatal **myocardial infarction** 40 days after the first dose of albiglutide. An autopsy was not performed.

Subject 8410486006: 61-year old male with a history of hypertension and dyslipidemia experienced an **acute myocardial infarction** on day 86 and died from cardiopulmonary arrest.

Subject 7062754999: 66-year old male with a history of chronic obstructive pulmonary disease, ischemic heart disease, hypertension, atrial fibrillation dyslipidemia, and myocarditis developed unstable angina and **acute myocardial infarction** resulting in death on study day 58.

***Reviewer Comment: There were 3 cases of fatal myocardial infarction in the albiglutide group within 90 days of receiving study medication (Subjects 3308179024, 8410486006, and 7062754999). All subjects had underlying risk factors of hypertension and dyslipidemia. Subjects 7062754999 also had a history of, ischemic heart disease. Although a temporal relationship of myocardial infarction events and initiation of study drug cannot be excluded the underlying cardiovascular risk factors confound assessment of causality. Cardiovascular (CV) deaths were adjudicated and evaluated in the CV meta-analysis (See Biostats review by Dr. Bo Li).***

#### Post-Therapy Albiglutide Death Narratives (P3-ISP)

3 subjects had post-therapy fatal SAEs in the albiglutide arm vs.1 post-therapy death in all comparators.

Subject 7061754909: 67-year old male with a history of hypertension, impotence,

and gastroesophageal reflux disease and myocardial infarction was found on day 773 to have a pathologic fracture of the right humerus for which study drug was withdrawn. Biopsy of the bone revealed adenocarcinoma of the lungs with bony metastasis. The subject died on study day 876. The preferred term was **bone neoplasm malignant**.

***Reviewer Comment: Follow-up information requested from the sponsor noted that the event term was updated from 'bone neoplasm malignant' in the original BLA to 'lung adenocarcinoma metastatic' and the case was initially classified as post therapy in IAS but reclassified as on-therapy in the 4MSU. The subject reported a past history of tobacco use at study screening having stopped smoking in 1989. A history of prior malignancy was not reported and information regarding occupational exposure or family history was not specifically collected. Source documents did not provide any additional relevant history or suspected risk factors.***

Subject 344575391: 71-year old female with a past medical history of asthma, dyslipidemia, and hypertension died 597 days after the first dose of investigational product and 209 days after the last dose of study medication. The cause of death was **unknown**.

Subject 7063753994: 71-year old female abdominal obesity, peripheral neuropathy, osteoarthritis, restless leg syndrome, hypertension, and dyslipidemia. Was found to have **metastatic cancer to the liver of unknown primary** 377 days after the first dose of study medication and 265 days after the study medication was withdrawn for dysguesia. According to the death certificate, the primary cause of death was cerebrovascular accident .

***Reviewer Comment: A follow-up information request clarified that the spleen, pancreas, kidneys and bowels were unremarkable on CT imaging. In addition a prior chest-X-ray and gastroscopes were clear. She had negative alpha fetoprotein and carcinoembryonic antigen. Additional imaging, colonoscopy and oncology consultation were pending at the time of death. Therefore the etiology of the primary malignancy remained unknown.***

#### FOUR MONTH SAFETY UPDATE (4MSU) DEATHS

At the 4 months safety update there were 3 additional on-therapy deaths in the albiglutide treatment group and 4 in all comparators.

#### **Table 32: P3-ISP - On-Therapy Fatal Serious Adverse Events Reported During the 4 Month Safety Update**

	All comparators	Albiglutide
<b>SOC</b>	N =1595	N =1427
Preferred Term	N (%)	N (%)
Any Event	4 (0.3)	3 (0.2)
<b>Neoplasms</b>		
Any Event	1 (0.1)	2 (0.1)
Bile duct cancer	0	1 (0.1)
Prostate cancer metastatic	0	1 (0.1)
Lung neoplasm malignant	1 (0.1)	0
<b>General disorders</b>		
Any Event	0	1 (0.1)
Death	0	1 (0.1)
<b>Cardiac disorders</b>		
Any Event	1 (0.1)	0
Acute coronary syndrome	1 (0.1)	0
<b>Infections and infestations</b>		
Any Event	1 (0.1)	0
Peritonitis	1 (0.1)	0
<b>Uncoded</b>		
Any event	1 (0.1)	1 (0.1)
Acute myocardial infarction temporally related to surgical	0	1 (0.1)
Death – heart attack	1 (0.1)	0

Source 120 Day Safety Update Table 7, Page 56

## Death Narratives (4MSU)

### On-therapy Albiglutide Death Narratives (4MSU)

Subject 3403757986: 70-year-old male with a history colon adenoma and benign prostate hypertrophy was diagnosed with **bile duct cancer** 996 after the start of investigational product, which resulted in death approximately 7 months later. The subject was a former smoker with a history of heavy alcohol consumption in the 1970 and 1980. EGD/EUS and colonoscopy failed to show any primary lesion. Significant laboratory values included at the time of the event were: alkaline phosphatase (137 U/L [normal range: 20 to 125]), gamma-glutamyltransferase (140 U/L [normal range: 0 to 75]), HDL (34 U/L [normal range >34 U/L]), and lipase (62 U/L [normal range: 7 to 60]). Endoscopic ultrasonography revealed a normal appearing pancreas. Review of chemistry data in the CSR revealed an elevated baseline GGT of 99 U/L [normal range: 0 to 75] and an elevated AST 132 U/L [normal range 0-55 U/L] on study day 624 (baseline AST values not provided)

**Reviewer Comment: A review of the CIOMS form indicated that oncology consultation prior to the subject's death indicated that histologically his tumor**

***most likely represented a gastric or pancreatic primary. An information request was sent to the sponsor for additional information regarding the primary origin of the malignancy. The sponsor noted that although the early assessments suggested the primary malignancy to be gastric or pancreatic, further work up led to the diagnosis of cholangiocarcinoma with the primary site of malignancy remaining unknown. In addition review of the subject's medical records did not suggest a history of risk factors for bile duct cancer (primary sclerosing cholangitis, bile duct stones or cysts). There was no information regarding parasitic exposures or travel to areas endemic with liver fluke (Asia).***

Subject 3499755989: 75 year old man with a history of prostate cancer experienced a **myocardial infarction** resulting in death 1128 days after the start of investigational product and 45 days since the last dose.

Subject 7063753919: 61 year old female with a history of hypertension and dyslipidemia died 918 days after first dose (7 days after the last dose) of study drug of **unknown** cause.

#### Post therapy Albiglutide Death Narratives (4MSU)

There were 5 additional deaths in both the albiglutide and all comparators group. The applicant was asked to clarify the post-therapy follow-up period.

Subjects were followed >56 days after the last dose of study medication per protocol for the Phase III studies. SAEs were collected from the time the subject consented to participate in the study through week 164 or the final follow-up visit for subjects who discontinued active participation in the study (i.e., those who discontinued study medication but continued to be followed annually for up to 3 years for long-term cardiovascular safety assessment). In the case of the 5 subjects (with post-therapy deaths during the 4MSU, 4 discontinued active participation but remained in the study for annual follow-up (Subjects 7566757986, 7065754914, 3569754986 and 3458754988) and 1 subject (Subject 3672754982), completed 3-years of treatment with study medication but died before completing the 8 week follow-up visit.

Brief descriptions of deaths in the albiglutide group are detailed below.

Subject 3458754988: 73-year-old male died of **unknown** causes 697 days after the start of study drug, and approximately 411 days after the last dose.

***Reviewer Comment: Follow up information received from the applicant clarified the preferred/verbatim term for death to be death/death natural causes.***

Subject 3569754986: 63 year old female with a history of COPD and cardiac disease died on day 1133 of **unknown** causes.

**Reviewer Comment: Follow up information requested from the sponsor indicated the preferred term/ verbatim term cause of death to be “chronic obstructive pulmonary disease exacerbation.” Additional details were not provided.**

Subject 3672754982: 55-year-old male subjects with a history of hypertension died of **sudden death** three years after the start of study drug. The cause of death was determined to be coronary atherosclerotic disease.

**Reviewer Comment: The applicant updated the preferred term for the fatality to be “coronary artery disease.”**

Subject 7065754914: 62 year old female experienced **sudden death** of unknown cause on day 1103 after the start of investigational drug and 17 days after the last dose the subject.

Subject 7566757986: 59-year-old male died of an **acute myocardial infarction** 880 days after the first dose and 271 days after the last dose of study drug.

**Reviewer Comment: Several of the post therapy death narratives lacked adequate clinical details to determine the exact cause of death.**

## CUMULATIVE DEATHS

The overall incidence of death was comparable for albiglutide compared to all comparators (0.9% vs. 1.0%, respectively). The event density, through the 4MSU data cutoff date for on-therapy deaths in the integrated studies was 0.53 AEs/100 person-years in the albiglutide treatment group and 0.51 AEs/100 person-years in the all comparators treatment group, which represents a slight increase over that reported in the original BLA. Cumulative data demonstrated that the neoplasms SOC had the highest proportion of deaths for both treatment arms (0.3% albiglutide vs. 0.4% all comparators). Most subjects had single events, except 2 subjects in the albiglutide group had fatal lung cancer related events. There was a higher number of lung cancer related fatalities in all comparators when combining events of metastatic, malignant and non-small cell lung cancer.

## RENAL STUDY (GLP114130) DEATHS

There were 4 on-therapy deaths in both the albiglutide and the sitagliptin arm. Brief descriptions of deaths in the albiglutide group are described below and in Table 33

**Table 33: Renal Study (GLP114130) Fatal Adverse Events by Subject: Overall Data (Safety Population)**

Subject ID	Age (yr.)/ Sex/ Race	Preferred Term	Time Since First Dose/Time
<b>Albiglutide</b>			
1140130001	79/ Male/ White	Pleural mesothelioma	309 / 3
1255130002	73/ Male/ White	Pancreatic pseudocyst	168 / 1
1460130003	65/ Male/ White	Sudden cardiac death	312 / 11
5605130005	72/ Male/ Black	Cardiac disorder	184 / 23
<b>Sitagliptin</b>			
3101130002	66/ Female/ White	Ischemic stroke	404 / 47
3101130005	62/ Female/ White	Subarachnoid hemorrhage	227 / 3
3304130009	82/ Female/ Other	Malignant melanoma	42 / 4
5615130015	77/ Female/ Black	Gastroenteritis	284 / 18

Source CSR GLP114130 Table 50, Page 164. yr. = years.

Death Narratives (Renal Study)

On-therapy Albiglutide Death Narratives (Renal Study)

Subject 1140130001: 80 year old man with history of tobacco use, alcohol consumption, colon cancer and moderate renal impairment (eGFR 45 ml/min) was diagnosed with **malignant pleural mesothelioma** on study day 309. The subject died 3 months later and the exact cause of death is unknown.

**Reviewer Comment: Follow-up information was requested and the applicant notes that the subject had a 50 pack year tobacco history and worked previously as (b) (4) and had extensive prior asbestos exposure. Determination of**

***study drug causality is confounded by the strong relationship between asbestos exposure and the development of mesothelioma.***

Subject 1255130002: 73-year old male with a past medical history of hypertension, dyslipidemia and chronic renal insufficiency and basal cell carcinoma was found to have an incidental finding of 2 new pancreatic cysts 3 months after the start of study drug. On study day 159 he underwent an endoscopic ultrasound and fine-needle aspiration of the pancreatic cyst and developed post procedure acute pancreatitis (lipase 4895 (73-393). On study day 168 CT imaging showed worsening pancreatitis with a new 6 cm pseudocyst. He subsequently developed severe necrotizing pancreatitis, life-threatening septic shock and severe multi-organ failure and was placed on comfort care. The events pancreatitis, **pancreatic pseudocyst** and pancreatitis necrotizing were adjudicated by the Pancreatitis Endpoint Committee and were considered to be unlikely attributable to investigational product.

***Reviewer Comment: The likely cause of death is post ERCP necrotizing pancreatitis resulting in sepsis and multi-organ failure.***

Subject 1460130003: 65-year old male with moderate renal impairment (eGFR 38 ml/min), congestive heart failure, and coronary artery disease developed atrial fibrillation on day182. On day 312 he experienced **sudden cardiac death** of unknown etiology

Subject 5605130005: 72 year old man with moderate renal failure (eGFR 32 ml/min) was found on study day 154 to have new ischemic changes on his EKG. He died on study day 184 of unknown cause. The death was attributed to **cardiac disorder**.

In the sitagliptin groups there were 4 deaths: ischemic stroke, subarachnoid hemorrhage, **malignant melanoma** and gastroenteritis.

### **7.3.2 Non-fatal Serious Adverse Events (SAEs)**

The overall proportion of non-fatal SAEs was similar between subjects treated with albiglutide (10.6%) and all comparators (10.3%). The system organ classes with the most events in the albiglutide arm were in the infections and infestations disorders, cardiovascular and gastrointestinal SOCs. On-therapy SAEs (by preferred term) that occurred in  $\geq 4$  subjects in the albiglutide group with a higher proportion of subjects ( $> 2$  fold higher) than all comparators were events of pneumonia, gastroenteritis, appendicitis, asthma, atrial fibrillation, transient ischemic attack, myocardial infarction and cerebrovascular accident.

Cumulative data demonstrated that adverse events were balanced between groups (12.4% (262/2116) in the albiglutide arm and 12% (273/2284) in all comparators). A higher proportion of adverse events in the albiglutide group occurred in the infections

and cardiac disorders SOCs. The individual preferred terms accounting for imbalances that were not in favor of albiglutide were for events of pneumonia, atrial fibrillation, asthma, appendicitis, myocardial infarction and transient ischemic attacks.

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

#### Albiglutide vs. Placebo

The overall incidence of non-fatal SAEs was greater in the placebo group (12.8%, 60/468) vs. albiglutide treated subjects (10.5%, 97/923). Most events in the albiglutide arm occurred in the cardiovascular disorders SOC [2.4%, 22/923 albiglutide treated vs. 3%, 14/468 in placebo] and infections/ infestations disorders SOC [2.2%, 20/923 albiglutide vs. 2.1%, 10/468 placebo treated subjects].

Preferred term events occurring in  $\geq 0.2\%$  of albiglutide treated subjects with a higher incidence compared to placebo were for events of atrial fibrillation, angina pectoris, appendicitis, gastritis, abdominal hernia, pancreatitis, small intestinal obstruction, vomiting, convulsions, hypertensive crisis and pneumonia.

#### Albiglutide vs. All Comparators

Pooled data comparing albiglutide to all comparators was reviewed and are summarized in

Table 34 for non-fatal SAEs by MedDRA SOC. The table represents subjects with at least 1 SAE in the albiglutide arm and where the incidence was higher in the albiglutide group compared with comparators.

The overall proportion of non-fatal SAEs was similar between subjects treated with albiglutide (10.6%) and all comparators (10.3%). The system organ classes with the most events in the albiglutide arm were in the infections and infestations disorders, cardiovascular and gastrointestinal SOCs.

On-therapy SAEs (by preferred term) that occurred in  $\geq 4$  subjects in the albiglutide group with a higher proportion of subjects ( $> 2$  fold higher) than all comparators were events of pneumonia, gastroenteritis, appendicitis, asthma, atrial fibrillation, transient ischemic attack, myocardial infarction and cerebrovascular accident.

The cardiovascular safety of albiglutide was evaluated through the CV meta-analysis (See Dr. Bo Li's statistical review). SAEs for pancreatitis, thyroid cancer, liver events, injection site reactions, systemic allergic reactions, hypoglycemia, diabetic retinopathy and gastrointestinal events are adverse events of special interest (AESI) that are also discussed separately (7.3.4).

**Table 34: Non-fatal Serious Adverse Events by MedDRA System Organ Class and Preferred Term with At Least 1 Events in the Albiglutide arm and a Higher Incidence Compared to All-comparators**

System Organ Class	All Comparators (N=2284) n	%	Albiglutide (N=2116) n	%
	<b>235</b>	<b>10.3</b>	<b>224</b>	<b>10.6</b>
<b>Infections and infestations</b>				
Any Event	38	1.7	56	2.6
Pneumonia	2	0.1	9	0.4
Gastroenteritis	3	0.1	5	0.2
Appendicitis	0		4	0.2
Bronchitis	0		3	0.1
Lobar Pneumonia	1	0	3	0.1
Osteomyelitis	1	0	3	0.1
Infection	0		2	0.1
Tracheobronchitis	1	0	2	0.1
Urinary tract infection	1	0	2	0.1
Viral infection	0		2	0.1
Appendicitis perforated	0		1	0
Bacterial pyelonephritis	0		1	0
Bronchopneumonia	0		1	0
Cellulitis staphylococcal	0		1	0
Encephalitis herpes	0		1	0
Epiglottitis	0		1	0
Eye abscess	0		1	0
Hepatitis B	0		1	0
Influenza	0		1	0
Pancreatitis viral	0		1	0
Perirectal abscess	0		1	0
Pneumonia viral	0		1	0
Sepsis	0		1	0
Sinusitis	0		1	0
Staphylococcal infection	0		1	0
Tuberculosis	0		1	0
Viral pericarditis	0		1	0
<b>Cardiac disorders</b>				
Any Event	48	2.1	49	2.3
Atrial fibrillation	2	0.1	9	0.4
Angina unstable	7	0.3	7	0.3
Myocardial infarction	3	0.1	5	0.2
Arteriosclerosis coronary Artery	0		3	0.1
Angina pectoris	0		2	0.1
Atrial flutter	0		2	0.1
Ventricular tachycardia	1	0.0	2	0.1
Arteriospasm coronary	0		1	0
Bradycardia	0		1	0

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Cardiac failure	1	0.0	1	0
Cardiomyopathy	1	0.0	1	0
Congestive cardiomyopathy	0		1	0
Pericardial effusion	0		1	0
Sinus bradycardia	0		1	0
<b>Gastrointestinal disorders</b>				
Any event	20	0.9	23	1.1
Gastritis	0		3	0.1
Pancreatitis	1	0	3	0.1
Abdominal hernia	0		2	0.1
Colitis ischemic	0		2	0.1
Lower gastrointestinal hemorrhage	0		2	0.1
Small intestinal obstruction	1	0	2	0.1
Vomiting	0		2	0.1
Abdominal pain	0		1	0
Constipation	0		1	0
Diarrhea	0		1	0
Gastrointestinal hemorrhage	0		1	0
Gastroesophageal reflux disease	0		1	0
Hiatus hernia	0		1	0
Pancreatitis acute	1	0	1	0
Sigmoiditis	0		1	0
<b>Nervous system disorders</b>				
Any Event	22	1.0	23	1.1
Transient ischemic attack	3	0.1	7	0.3
Cerebrovascular accident	3	0.1	6	0.3
Migraine	1	0	3	0.1
Carpal tunnel syndrome	0		2	0.1
Syncope	1	0	2	0.1
Hypoaesthesia	0		1	0
Polyneuropathy	0		1	0
<b>General Disorders</b>				
Any Event	23	1	19	0.9
Non-cardiac chest pain	4	0.2	5	0.2
Device leakage	0		1	0
Device malfunction	0		1	0
<b>Neoplasms benign, malignant and unspecified</b>				
Any Event	29	1.3	19	0.9
Acute myeloid leukemia	0		2	0.1
Bladder cancer	0		1	0

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Hepatic neoplasm malignant	0		1	0
Hodgkin's disease	0		1	0
Lung neoplasm	0		1	0
Lung squamous cell carcinoma stage	0		1	0
Meningioma	0		1	0
Neuroendocrine tumor	0		1	0
Ovarian germ cell teratoma	0		1	0
Pheochromocytoma	0		1	0
Pituitary tumor benign	0		1	0
Uterine leiomyoma	0		1	0
<b>Musculoskeletal and connective tissue disorders</b>				
Any event	26	1.2	18	0.9
Intervertebral disc protrusion	1	0	2	0.1
Costochondritis	0		1	0
Intervertebral disc degeneration	0		1	0
Muscle spasms	0		1	0
Pathological fracture	0		1	0
Spondylolisthesis	0		1	0
Trigger finger	0		1	0
<b>Injury, poisoning and procedural</b>				
Any Event	18	0.8	17	0.8
Road traffic accident	0	0	2	0.1
Thoracic vertebral	0		2	0.1
Arterial injury	0		1	0
Concussion	0		1	0
Femur fracture	1	0	1	0
Head injury	1	0	1	0
Heat stroke	0		1	0
Hip fracture	0		1	0
Incisional hernia	2	0.1	1	0
Intentional overdose	0		1	0
Joint dislocation	0		1	0
Ligament rupture	0		1	0
Meniscus lesion	0		1	0
Post procedural hemorrhage	0		1	0
Rib fracture	0		1	0
<b>Renal and urinary disorders</b>				
Any Event	9	0.4	11	0.5
Hydronephrosis	0		2	0.1
Renal failure acute	1	0	2	0.1
Azotemia	0		1	0
Calculus urinary	0		1	0
Renal colic	0		1	0

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<b>Vascular disorders</b>				
Any Event	8	0.4	11	0.5
Deep vein thrombosis	1	0	3	0.1
Hypertensive crisis	0		2	0.1
Aortic aneurysm	0		1	0
Arteriosclerosis	0		1	0
Diabetic vascular disorder	0		1	0
Femoral arterial stenosis	0		1	0
Malignant hypertension	0		1	0
Peripheral ischemia	0		1	0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Any event	11	0.5	10	0.5
asthma	1	0	4	0.2
Pulmonary embolism	1	0	3	0.1
Atelectasis	0		1	0
Chronic obstructive	0		1	0
Pleural effusion	0		1	0
Respiratory distress	0		1	0
<b>Psychiatric disorders</b>				
Any event	5	0.2	6	0.3
Depression	0		2	0.1
Bipolar disorder	0		1	0
Confusional state	0		1	0
Panic disorder	0		1	0
Suicidal ideation	0		1	0
<b>Blood and lymphatic system disorders</b>				
Any Event	0		4	0.2
Anemia	0		2	0.1
Lymphadenopathy	0		1	0
Thrombocytopenia	0		1	0
<b>Hepatobiliary disorders</b>				
Any Event	7	0.3	4	0.2
Cholecystitis	0		1	0
Cholecystitis chronic	0		1	0
Drug-induced liver injury	0	0	1	0
<b>Reproductive disorders</b>				
Any Event	4	0.2	4	0.2
Cervical cyst	0		1	0
Cervical polyp	0		1	0
Ovarian cyst	0		1	0
<b>Eye disorders</b>				
Any Event	4	0.2	3	0.1

Angle closure glaucoma	0		1	0
Cataract	0		1	0
<b>Metabolism and nutrition disorders</b>				
Any Event	6	0.3	3	0.1
Hyperglycemia	0		2	0.1
Hypokalemia	0		1	0
<b>Ear and labyrinth</b>				
Any Event	1	0	2	0.1
Vertigo	1	0	2	0.1

Modified from ISS Table SP3-19.1.1, Page 10447.

#### FOUR MONTH SAFETY UPDATE (4MSU) NON-FATAL SERIOUS ADVERSE EVENTS

During the safety update period non-fatal SAEs were slightly higher in the albiglutide group (4.2%, 60/1427) vs. all comparators (3.6%, 57/1595). The highest proportion of SAEs in the albiglutide group occurred in the Infections/infestation SOC (1.1%, n=16) vs. all comparators (0.5%, n=8). Most events in the infections SOC for albiglutide treated subjects were single event terms. Pneumonia events were balanced between groups (0.3%, in both treatment arms).

SAEs of special interest are discussed in their respective section under submission specific primary safety concerns Section 7.3.5.1.

#### CUMULATIVE NON-FATAL SERIOUS ADVERSE EVENTS

Overall adverse events were balanced between groups (12.4% (262/2116) in the albiglutide arm and 12% (273/2284) in all comparators). A higher proportion of adverse events in the albiglutide group occurred in the infections and cardiac disorders SOCs. The individual preferred terms accounting for imbalances that were not in favor or albiglutide were for events of pneumonia, atrial fibrillation, asthma, appendicitis, myocardial infarction and transient ischemic attacks. The event of *myocardial infarction* was numerically higher in albiglutide treated subjects (0.5%) vs. all comparators (0.1%). However the event term of *acute myocardial infarction* was higher in all comparators (0.6%) vs. the albiglutide arm (0.3%). Transient ischemic attack occurred in 0.4% (8/2116) of albiglutide treated subjects and 0.2 (5/2284) comparators. Cerebrovascular SAEs were balanced between albiglutide and all comparators (0.3%, 6/2116 and 0.2%, 2/2284, respectively). Ischemic stroke events were balanced (1 event in albiglutide 1/2116 and 2/2284 in comparators). A single event of hemorrhagic stroke occurred in the comparator group.

## **Asthma Events**

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

#### Albiglutide vs. Placebo

There were no serious adverse asthma events in either treatment comparison grouping.

#### Albiglutide vs. All Comparators

A higher incidence of serious asthma events were reported in albiglutide subjects (4 subjects, 0.2%) vs. the all comparator group (1 subject). Review of case narratives for 3 of these subjects (1002486010, 1257486004, and 7063754921) revealed that all had a history of underlying asthma. Event onset ranged between study day 216 and 348, and all subjects were hospitalized and required steroid treatment. Mechanical ventilation was not required for any subjects, and while study medication was held for 2 subjects during hospitalization there were no withdrawals.. Of the 4 cases of asthma SAEs, 1 case occurred in an antibody positive subject.

One antibody positive subject experienced a serious asthma event and also had urticaria and is described in detail below.

Subject 3672754982: 55 year old man with a history of asthma, seasonal allergies and hypertension experienced urticaria on study day 20 and an acute exacerbation of **asthma** on study day 68. The subject complained of throat tightness and hives on his arms at the time of the asthma event. He was hospitalized and treated with IV steroids. Prior to admission he complained of cough and productive sputum. No action was taken with the study medication and the subject was discharged 4 days later. On study days 20 and 168 the subjects developed urticaria treated with antihistamines. Additional details regarding the rash were not provided in the narrative. On study day 375 he developed shortness of breath and was found to have triple vessel cardiac disease and underwent percutaneous trans luminal coronary angioplasty. The subject tested positive for the antibody to albiglutide at week 104.

***Reviewer Comment: Although a relationship between the event of asthma exacerbation, urticaria and throat tightness cannot be excluded, the subject's underlying asthma history confounds determination of study drug causality.***

Narratives for single events of respiratory distress and chronic obstructive pulmonary disease (COPD) in albiglutide treated subjects were also reviewed. In both cases subjects had underlying history of respiratory conditions (asthma or COPD, respectively).

#### 4MSU (ASTHMA EVENTS)

There was one additional non-fatal serious event of asthma and one event of chronic obstructive pulmonary disease (COPD) in the albiglutide group vs. 0 in all comparators. These two events are described briefly below.

Subject 7063754921: 70 year old female with history of asthma and tobacco use developed an **asthma** exacerbation on study day 771 requiring hospitalization. The subject was subsequently also diagnosed with chronic obstructive pulmonary disease.

**Reviewer Comment: Narrative review indicates that this subject also had a non-fatal serious asthma event in the original BLA submission.**

Subject 3543753984: 65 year old male with a history of **COPD** and smoking developed a COPD exacerbation on study day 1074.

#### CUMULATIVE (ASTHMA EVENTS)

Overall cumulative non-fatal serious events of asthma occurred in a higher proportion of albiglutide treated subject 0.2% (4/2116) compared to 1 event in all comparators.

**Reviewer Comment: There was a small overall imbalance of serious asthma events not in favor of albiglutide (0.2%, 4/2116 vs. 1/2284). All events required hospitalization and steroid treatment. Most subjects experienced single events and there were no withdrawals from the study due to these events. Interpretation of study drug causality is limited by the fact that many subjects had underlying respiratory conditions. Asthma events should be monitored in future studies as a potential adverse event of interest in effort to further characterize any potential relationship with albiglutide.**

#### Appendicitis Events

##### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

##### Albiglutide vs. All Comparators

4 cases of appendicitis and 1 cases of perforated appendicitis occurred in albiglutide subjects (0.2%) vs. 0 in all comparators. Brief narratives of appendicitis events are delineated below.

- Subject 3779754986: 28-year old male on study day 210 experienced severe **appendicitis** with pathology revealing acute gangrenous appendicitis and periappendicitis.
- Subject 3644755986: 61-year old female experienced severe **perforated appendicitis** 222 days after the first dose of investigational product.

- Subject 1423486016: 40-year old female experienced acute suppurative **appendicitis** and underwent appendectomy on day 178 days.
- Subject 7661753988: 62-year old female developed acute phlegmonous ulcerative **appendicitis** with fibrotic/purulent periappendicitis on study day 653.
- Subject 3579753987: 59-year old female experienced severe **appendicitis** on study day 300.

#### 4MSU (APPENDICITIS EVENTS)

There was one additional case of appendicitis in the albiglutide group vs. 0 in all comparators.

- Subject 3774753980: 41 year old female developed acute **appendicitis** on study day 937.

#### CUMULATIVE (APPENDICITIS EVENTS)

Overall non-fatal serious events of appendicitis occurred in a higher proportion of albiglutide treated subject 0.2% (5/2116) compared to 0 in all comparators. In addition there was 1 case of perforated appendicitis in the albiglutide group.

***Reviewer Comment: There was an overall numeric imbalance in serious cases of appendicitis in the albiglutide group (n= 5/2116; 0.2%) vs. all comparators (0 cases). In addition there was one case of perforated appendicitis in the albiglutide group and 0 in all comparators. The majority of appendicitis events in the P3-ISP occurred in females ranging from 40-70 years of age. While the relationship between the development of appendicitis and albiglutide use has not been elucidated the imbalance in serious cases in the albiglutide arm and the potential serious consequences of appendicitis (including peritonitis and abscess formation) warrants inclusion in the product label as an adverse reaction.***

#### Pneumonia Events

##### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

##### Albiglutide vs. Placebo

An imbalance in events not favoring albiglutide was seen for preferred term events of pneumonia (0.8%, 7/923) vs. 1 case of lobar pneumonia in placebo.

##### Albiglutide vs. All Comparators

Infection related events were the most commonly reported SAEs among albiglutide treated subjects, and the second most commonly reported among all comparators. As described in Table 35 serious adverse events among the albiglutide treated subjects

included 13 cases of pneumonia and 3 cases of bronchitis compared to 3 cases of pneumonia in all comparators.

**Table 35: Serious Events in the Lower Respiratory Tract Infection HLT (P3-ISP All Comparator Grouping)**

HLT Preferred Term	All Comparators (N=2284)		Albiglutide (N=2116)	
	N (%)	# events/ AE Density	N (%)	# events/ AE Density
<b>Lower respiratory tract And lung infections</b>	3 (0.1%)	3/ 0.08	16 (.76%)	16/ 0.47
Pneumonia	2 (0.1%)	2/ 0.06	9 (0.4%)	9/ 0.27
Bronchitis	0	0	3 (0.1%)	3/ 0.09
Lobar pneumonia	1	1/ 0.03	3 (0.1%)	3/ 0.09
Bronchopneumonia	0	0	1 (0.1%)	1/ 0.03

Source: Modified from ISS Table 214, Page 631. 1. Density = no. of AEs per 100 patient years  
 HLT – high level term

As delineated in Table 36 all subjects experiencing serious events of pneumonia were hospitalized. Events were balanced between men (7/13) and women (6/13) and there was not a consistent pattern regarding date of onset with respect to study drug initiation. There majority of cases were community acquired except for one case of confirmed tuberculosis in South Africa for the event term “lobar pneumonia”. One subject required mechanical ventilation and developed transverse myelitis. The applicant notes that none of the events occurred in subjects who were anti-drug antibody positive. In addition, several cases of pneumonia were confounded with underlying pulmonary conditions such as asthma or chronic obstructive pulmonary disease. Two subjects had a known smoking history. However, many of the narratives lacked information regarding relevant risk factors.

The applicant notes that that the consistently higher incidence of respiratory events in the albiglutide group is considered to support a conclusion that pneumonia be included the proposed product labeling as an adverse reaction.

**Table 36: Serious adverse events of pneumonia**

Subject ID Age/ Sex Ethnicity Country	Preferred Term	Past Medical History Risk Factors	HPI and Clinical Presentation	Radiographic data	Time since 1st dose/ Time since last dose (d=day)	Maximum Intensity/ Withdrawn / Action Taken	Comments
3464753986 64/Male White USA	Pneumonia/ Pleural Effusion/ Bibasilar atelectasis	Former smoker	Coughing and shortness of breath x 1 day  Oxygen sat 78%	Chest CT - bibasilar atelectasis, small right pleural effusion  CXR - elevated right hemidiaphragm	740d/2d	Moderate/ No None	Hospitalized, no tachypnea and afebrile  <i>Reviewer Comment: It is unclear from the narrative if the subject had pneumonia</i>
7072754992 62/Female African South Africa	Lobar pneumonia	GERD	WBC 17.9 (nml 4-10 x 10 <sup>9</sup> /L)	x-rays were performed (results not reported)	353d/3d	Moderate/ No/ None	Hospitalized and treated with antibiotics  <i>Reviewer Comment: This narrative lacks relevant radiographic test results</i>
3495754980 60/ Female White USA	Lobar pneumonia	Chronic bronchitis and asthma  GERD	Cough, shortness of breath x 4 mths 2 days of cough and green sputum production Fever (103 F)	CXR - left lower lobe pneumonia.	597d/4d	Severe/ No/ Study drug interrupted for 2 weeks	Hospitalized with complication of hypotension (blood pressure 83/35 mmHg). Treated with antibiotics, fluids and dopamine. Blood cultures were negative.
3663754981 60/Male White UA	Pneumonia	Smoker x 24 years (quit 1992) asbestos exposure, GERD	3 days of non-productive cough and shortness of breath. Fever of 102F	CXR- bilateral infiltrates suggestive of pneumonia	133d/1d	Moderate/ no/ none	Hospitalized and treated with antibiotics
3442754902 66/Female White USA	Pneumonia	Sleep apnea	Generalized weakness, low grade fever, chills, and dry	CXR- left lower lobe infiltrate	906d/3d	Moderate/ no/ none	Hospitalized. The subject had <i>rhabdomyolysis</i> thought to be due to being on the floor for 6 to 7 hours after he had fallen to the

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			cough. 102.5 °F WBC 17.6 (4.8 -10 k/uL)				ground due to weakness. The subject experienced an event of <i>atrial fibrillation</i> and was pharmacologically cardioverted
7062754980 58/ Male White South Africa	Atrial fibrillation  Broncho-pneumonia	Episode of bronchitis diagnosed 2 month prior	Sputum culture negative TB negative	CXR – bronchopneumonia	734d/5d  748d/5d	Moderate/ no/none	2 weeks prior the subject was found to have atrial fibrillation and was pharmacologically treated.
3709753980 68 Male White USA	Pneumonia		Intermittent fever, cough, and renal insufficiency secondary to urine retention due to benign pr Occasional gram positive cocci and rare gram positive rods. WBC 11.5 (3.7-10.4 K-CM) Seg bands (10 (1.5-6.1 K-CM)	CXR- bilateral ill-defined infiltrates and opacities	363d/5d	Moderate/ No/ Dose interrupted for 2 days	Hospitalized and treated with antibiotics
3596755987 59 White Male USA	Pneumonia	GERD	Fatigue, chills T102.5F	CXR- left lower lobe infiltrate	304d/10d	Moderate/ No/ None	Hospitalized and treated with antibiotics
3653755981 63 White Male USA	Pneumonia	Intermittent chronic bronchitis, chronic obstructive pulmonary disease, intermittent shortness of breath,	Productive cough for 24 to 48 hour	CXR - right upper lung infiltrate	168d/6d	Severe/ No/None	Hospitalized. Treated with antibiotics. Developed atrial fibrillation 2 days after hospitalization.

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Albiglutide

		interstitial lung disease					
3535756980 55 Female Hispanic USA	Pneumonia		Not provided	Not provided	unknown	Severe/ No/ drug interrupted for 4 weeks	Hospitalized. <i>Review Comment: Clinical details are lacking</i>
3460757997 57 Male White USA	Pneumonia	Asthma	Not provided	Not provided	635d/2d	Moderate/ no/none	Hospitalized. Information was not provided
5604486005 48 Female Black South Africa	Lobar Pneumonia/ Tuberculosis	History lower respiratory tract infection (unknown etiology)	Not provided for lobar pneumonia	Chest x-ray confirmed right lower lobe pneumonia	286d/6d	MODERATE/ no/none	Hospitalized and treated with antibiotics. Found to have confirmed tuberculosis 2 weeks later.
7969757986 50 Female White Spain	Pneumonia		Lumbar/ neck pain x 5 days, fever	CXR -diffuse bilateral infiltrates in the pulmonary parenchyma. Thoracic angiogram - multiple bilateral patchy ground glass condensations of probable infectious etiology.	396d/27d	Moderate/ Yes/ Withdrawn 3 months later	<i>Hospitalized The subject required intubation and mechanical ventilation. The subject's hospital course was complicated with methicillin- resistant Staphylococcus aureus bacteremia worsening renal function, transverse myelitis (identified on MRI), quadriplegia, and urinary tract infection. Study drug was withdrawn. Follow-up spinal MRI demonstrated showed significant improvement when compared to the previous MRI</i>

Reviewer Generated from Case Narratives

Cases narratives for bronchitis and tracheobronchitis (2 subjects) were reviewed (subjects 3719754986, 3589754986, and 3465757988 (subject 3719754987 had a history of COPD and asthma). Subject 1001486015: 65 year old female had tracheobronchitis 362 days after the first dose of study drug. On study day 58 she experienced angioedema (lip swelling) and renal impairment attributed to lisinopril.

#### 4MSU (PNEUMONIA EVENTS)

At the time of the 4MSU non-fatal serious pneumonia events were balanced between albiglutide and all comparators (0.3%, 4/1427 and 4/1595, respectively). In addition there was 1 preferred term event of lobar pneumonia in the albiglutide group. Two subjects in each treatment group reported a second serious event of pneumonia (Subject 3709753980 and Subject 3653755981). All pneumonia events that occurred during the incremental period occurred in anti-albiglutide antibody negative subjects.

Subject 3511756986: 43 year old female without a pulmonary history developed lobar pneumonia and **acute respiratory failure** (requiring mechanical ventilation) approximately 3 years after study drug initiation and 20 day after the last dose.

#### CUMULATIVE (PNEUMONIA EVENTS)

Cumulative data supports the findings from the original BLA submission demonstrating an imbalance in serious pneumonia events in subjects treated with albiglutide. In total, pneumonia SAEs occurred for 16 subjects (0.8%) in the albiglutide treatment group representing 18 events and 7 subjects (0.3%) in the all comparators treatment group representing 7 events. Among these cases, 1 subject withdrew from active study treatment and 2 subjects reported a second serious on-therapy pneumonia event. In addition, all were anti-drug antibody negative. There were also 3 SAEs of bronchitis in the albiglutide treatment group versus none in the all comparators treatment group.

***Reviewer Comment: Albiglutide has been shown to bind to the FcRn receptor. The Fc receptor (FcRn), also known as the Brambell receptor, is a MHC class I like molecule that functions to protect IgG and albumin from catabolism. However a relationship between receptor binding and pneumonia events has not been elucidated.***

***The applicant states that the consistently higher incidence of pneumonia events (serious and non-serious) in the albiglutide group provides basis for the inclusion of pneumonia in the product labeling as an adverse reaction (Non serious events are discussed under Section 7.4.1. This reviewer agrees that the numeric imbalance in serious pneumonia events not in favor of albiglutide warrants inclusion in the product label. In addition in order to obtain a better***

***understanding of the nature of this relationship pneumonia should be included as an adverse event of special interest in future albiglutide trials.***

### **Atrial Fibrillation (AF) Events**

#### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

##### Albiglutide vs. Placebo

In the albiglutide vs. placebo comparison treatment grouping a higher proportion of adverse events occurred in the cardiac disorder SOC (2.4%, 22/923 vs. 3%%, 14/468). A greater proportion of subjects treated with albiglutide had events of atrial fibrillation (0.2%, 2/923 vs. in placebo.)

##### Albiglutide vs. All Comparators

While overall events in the cardiac disorders SOC were balanced (2.3%, 49/2116 from albiglutide vs. 2.1%, 48/2284 in all comparators), there was an imbalance for SAEs of atrial fibrillation (0.4%, 9/2116 for albiglutide vs. 0.1%, 2/2284 in all comparators). Atrial flutter events occurred in 2 subjects in the albiglutide groups and none of the subjects in the all comparators group.

##### Albiglutide SAE Narratives for Atrial Fibrillation and Atrial Flutter Events

Subject 3569754982: A 70-year old male with a history of ischemic heart disease without cardiomyopathy (coronary artery disease), congestive heart failure, chronic obstructive pulmonary disease, and obstructive sleep apnea developed **atrial fibrillation** on study 196. Cardiac evaluation did not identify a cause and the subject was successfully electrically cardioverted. No action was taken with study medication.

***Reviewer Comments: While a relationship to study drug cannot be excluded this subject has numerous risk factors for atrial fibrillation including; significant underlying cardiac disease, obstructive pulmonary disease and sleep apnea.***

Subject 3716754986: 77-year old male developed **atrial fibrillation** 660 days after the first dose of albiglutide. He was diagnosed with hyperthyroidism, TSH 4.63 (ULN 4.2).

***Reviewer Comment: The elevated TSH in this subject may be due to hypothyroidism or a rare cause of hyperthyroidism induced by excess TSH secretion. A diagnosis cannot be determined without additional thyroid function tests (which were not provided).***

Subject 7062754980 58-year old male with a past medical history of hypertension and obesity experienced **atrial fibrillation** 734 days after the first dose of albiglutide. Chest

X-ray was normal. The subject was medically treated and discharged. On study day 748 the subject was hospitalized for **bronchopneumonia**. No action was taken with the study medication for either event

**Reviewer Comment: Although the initial Chest X-ray was normal it is possible that the subject may have had underlying pneumonia at the time of the atrial fibrillation event which was not yet evident on radiographic imaging. The narrative is lacking information regarding fever and clinical symptoms at the time of the arrhythmia event that may suggest an underlying infection.**

Subject 3652756986: 69-year old white male with a history of atrial fibrillation was hospitalized for **atrial fibrillation** on study day 112. The subject was initially diagnosed with atrial fibrillation during screening and underwent cardioversion prior to initiating study drug. The subject was treated with medical management. No action was taken with the investigational product

Subject 3465757988: 68-year old white male with a history of ischemic heart disease with cardiomyopathy, hypertension, and chronic kidney disease stage III developed sick sinus syndrome on study day 430 and underwent dual chamber permanent pacemaker placement. On study day 496 days he experienced **atrial fibrillation** and was cardioverted. No action was taken with the study medication

**Reviewer Comment: This case is confounded by the fact that atrial fibrillation is an atrial tachyarrhythmia associated with sick sinus syndrome.**

Subject 1021179002: 76-year-old male with a history of recurrent atrial fibrillation experienced recurrent paroxysmal **atrial fibrillation** on study day 145. He was hospitalized and successfully electrically cardioverted. No action was taken with albiglutide as the subject completed the treatment period.

Subject 1270179022: 57-year old male with a history of irregular heart beat and coronary artery disease developed **atrial fibrillation** 137 days after the first dose of albiglutide. The subject was taking an over-the-counter decongestant at that time for cough and congestion, and a 2-week history of sore throat and fever. The subject was found to have bronchopneumonia at the time of the event.

**Reviewer Comment: A determination of study drug causality is confounded in this case by the simultaneous occurrence of bronchopneumonia which could be a risk factor for arrhythmia development. In addition there is lack of information regarding the history of "irregular heart beat".**

Subject 1060486001: 57-year old female with a history of bipolar disorder, palpitations for 1 year, asthma and rheumatoid arthritis developed **atrial fibrillation** 277 days after

the first dose of albiglutide. The subject was hospitalized and medically treated. No action was taken with study medication.

Subject 3309486009: 57-year old male with past history of left anterior hemiblock developed **atrial fibrillation** 321 days after the first dose of study medication. He was hospitalized and medically cardioverted. Study medication was interrupted for 3 days. Cardiac work up was unremarkable.

Subject 1030179006 66-year old male with a history of **atrial flutter** experienced recurrent atrial flutter and was hospitalized 27 days after the first dose and 3 days after the fifth dose of albiglutide. Pulmonary and cardiac evaluations were unremarkable. No action was taken with the study medication and the event resolved with medical management.

**Reviewer Comment: Although the event occurred shortly after starting study drug, the subject's underlying history of arrhythmia limits any assessment of study drug causality.**

Subject 3442754908: 59-year old female with a history of deep venous thrombosis of the left leg experienced **atrial flutter** 159 days after the first dose of albiglutide. The subject was hospitalized and lung ventilation/perfusion scan was performed that showed no definite perfusion or ventilation defects and a low probability for pulmonary embolism. The subject was successfully cardioverted and study drug was interrupted for 4 days. The subject had numerous injection site reactions (>90) described as redness and itching. No action was taken for study medication.

#### 4MSU (AF EVENTS)

At the time of the update 1 subject had a SAE of atrial fibrillation in both treatment groups.

#### CUMULATIVE (AF EVENTS)

In the albiglutide group, 0.5% (10/2116) of subjects vs. 0.1% (3/2284) in comparators experienced non-fatal SAEs of atrial fibrillation. In addition 2 subjects in the albiglutide group vs. 0 in all comparators had events of atrial flutter.

**Reviewer Comment: Although many of the arrhythmia events occurred within 200 days of starting study drug. In the majority of cases subjects were hospitalized for medical management. Many subjects experiencing serious on-therapy events of atrial fibrillation and flutter had a history of arrhythmia or other contributory risk factors that confound an assessment of study drug causality. However, upon review of the totality of data at the time of BLA submission the applicant identified these arrhythmia events as an important identified risk and proposed**

***label atrial fibrillation/flutter as an adverse reaction. Following review of the data (serious and non-serious (See Section 7.4.1) this reviewer agrees with the applicant's decision to include atrial fibrillation/flutter in the labeling for albiglutide.***

### **Transient Ischemic Attacks (TIA)**

#### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

##### Albiglutide vs. Placebo

TIA events were balanced between albiglutide (0.2%, 2/923) and placebo treated subjects (0.2%, 1/486).

##### Albiglutide vs. All Comparators

A small imbalance not in favor of albiglutide was noted when compared to all comparators (0.3%, 7/2116 vs. 0.1%, 3/2284). Cerebrovascular events occurred in a higher proportion of albiglutide treated subjects (0.3%, 6/2118 vs. 0.1%, 3/2284). Events coded as ischemic stroke occurred in 1 albiglutide treated subject and 2 comparators. Single events of hemorrhagic stroke and cerebral infarction occurred in the all comparators group with no events in the albiglutide arm

***Reviewer Comment: Review of case narratives of albiglutide treated subjects did not reveal a consistent pattern. Events occurred in 4 men and 3 women with onset dates ranging from study data 135 to 728. All subjects had underlying risk factors for cardiovascular disease. There were no withdrawals from events of TIAs. Although TIA events were not a study endpoint in the CV meta-analysis, all reported TIA events were reviewed by the clinical endpoint committee (CEC) to ensure that stroke events had not been missed. One subject had a reported stroke after and one prior to the TIA. In the CV meta-analysis adjudicated events for stroke did not demonstrate a clinically relevant increased risk for albiglutide. Stroke events are discussed separately in Dr. Bo Li's review of the CV meta-analysis.***

##### 4MSU (TIA EVENTS)

TIA incidence was balanced between albiglutide and all comparators (0.1% in both arms). CVA events occurred in 0.1% of all comparators and no albiglutide treated subjects.

##### CUMULATIVE (TIA EVENTS)

TIA events occurred on 0.4% (8/2116) of albiglutide treated subjects and 0.2% (5/2284) of comparators. Cerebrovascular SAEs were balanced between albiglutide and all comparators (0.3%, 6/2116 and 0.2%, 2/2284, respectively). Ischemic stroke events were balanced (1 event in albiglutide 1/2116 and 2/2284 in comparators. A single event of hemorrhagic stroke occurred in the comparator group.

## Psychiatric Conditions

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

#### Albiglutide vs. Placebo

Overall psychiatric events were slightly higher in the albiglutide arm (0.3%, 3/923) compared to placebo (0.2%, 1/468). The events in the albiglutide arm were for single events of bipolar disorder, panic disorder and suicidal ideation.

#### Albiglutide vs. All Comparators

Overall psychiatric events were slightly higher in the albiglutide arm (0.3%, 6/2116) compared to placebo (0.2%, 5/2284). Most events were single preferred term events.. Subjects experiencing events of depression (3766754989, 3779754987) both had a medical history of depression. Similarly subjects in the albiglutide arm with single events of bipolar disorder, confusional state and panic disorder (3422757989, 3864754987, and 3755757988) had underlying psychiatric disorders.

One subject did not have a known psychiatric history and is described below.

Subject 5473753982: 49 year old with no known psychiatric history experienced **suicidal ideation** on study day 78. Psychiatric evaluation revealed home stressors and a one year history of mood fluctuations.

#### 4MSU (PSYCHIATRIC EVENTS)

One event of suicidal ideation was stated to have occurred in both the albiglutide and all comparators treatment arms.

However follow up information requested from the applicant noted that Subject 3504756998 did not have an adverse event of suicidal ideation and was incorrectly identified in the 4MSU. The correct subject ID was Subject 3681756980. The suicidal ideation event in Subject 3681756980 was reported as non-serious in the Original BLA and was subsequently upgraded to serious, and is described below.

Subject 3681756980: 40 year old male had **suicidal ideations** 478 days after starting investigational products. Additional information requested from the applicant revealed that the subject had a history of depression and insomnia and was under stress (unable to find a job, his son-in-law had committed suicide, and he was having family problems).

The following psychiatric events were also upgraded from non-serious at the time of the original BLA submission to serious with the 4MSU.

Subject 3616753986: 47 year old male with no known previous psychiatric history experienced **intentional overdose** of metformin 270 days after the first dose of study drug. The subject had started abusing alcohol one week prior to the event, and he was experiencing numerous stressors including loss of home and job, financial stressors and marital discord.

Subject 3694757981: 63 year old Asian male with a history a previous history of bipolar disorder and depression experienced **suicidal ideation** and Ambien overdose on study day 362.

#### CUMULATIVE (PSYCHIATRIC EVENTS)

Overall events were balanced between the albiglutide and all comparator treatment arms (0.3%, 7/2116 vs. 0.3% 6/2284). There were 2 subjects in the albiglutide group with serious events of suicidal ideation vs. 1 in all comparators. One subject in the albiglutide arm had an intentional overdose vs. 0 in comparators.

***Reviewer Comment: There was an overall small imbalance in suicidal ideation (intentional overdose) not in favor of albiglutide. However the sample size was small and two cases were confounded with underlying histories of depression and stressors.***

#### Anemia/Thrombocytopenia Events

##### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

Anemia and thrombocytopenia events were reviewed to identify any drug related etiology.

##### Albiglutide vs. All comparators (Anemia Events)

A slightly higher incidence of preferred term events of anemia occurred in the albiglutide group compared to all comparators (0.1% 2/2116 vs. 0). Events of anemia were reviewed and assessment of study drug causality was confounded by a recent surgical procedure in one case and anticoagulation with warfarin in another case.

**Reviewer Comment: Review of anemia narratives did not suggest a drug induced safety concern.**

Albiglutide vs. All comparators (Thrombocytopenia Events)

A single event of thrombocytopenia occurred in the albiglutide arm (0 in all comparators) and is described below.

Subject 3434754984: 62 year old female with a history of asthma, intermittent allergic rhinitis, hypertension, dyslipidemia, and a thyroid nodule developed **thrombocytopenia** on study day 796 (laboratory data is detailed in the table below). The subject presented to the ER with diffuses petechial, and reported taking esomeprazole/naproxen 500/20 starting 3 months prior to presentation with the last dose about 5 days prior to event onset. She was also found to be H. pylori positive. Hematology consultation noted severe thrombocytopenia with a differential diagnosis which included an idiopathic immune mediated phenomenon versus drug induced. Treatment included platelets, methylprednisolone, immune globulin and a prednisone taper. The study medication was interrupted for 2 weeks and the subject was discharged and the event of thrombocytopenia was considered resolved.

**Results from Laboratory Tests Performed**

Date	Blood Glucose /Glucose (plasma-efficacy) reference range: ULN = 5.5 mmol/L) <sup>a</sup>	Platelet Count (reference range: 130-400 GI/L) <sup>a</sup> (reference range: 140 - 440)	WBC (reference range: 3.8-10.8 GI/L) <sup>a</sup> (reference range: 4.6 - 10.0)
30 Jul 2009	7.9 <sup>a</sup>	235 <sup>a</sup>	11.7 <sup>a</sup>
27 Jul 2011	7.3 <sup>a</sup>	228 <sup>a</sup>	9.3 <sup>a</sup>
(b) (6) (hospitalizatio	246 <sup>b</sup>	1 <sup>b</sup>	12.3 <sup>b</sup>
(b) (6) (hospitalizatio		20 <sup>b</sup>	15.1 <sup>b</sup>
(b) (6) (hospitalizatio		32 <sup>b</sup>	26.0 <sup>b</sup>
(b) (6) (hospitalizatio		63 <sup>b</sup>	13.7 <sup>b</sup>
10 Oct 2011 (post discharge)		287 <sup>b</sup>	
26 Oct 2011	7.6 <sup>a</sup>	233 <sup>a</sup>	10 <sup>a</sup>

a. Values are from the central laboratory.  
 b. Values are from the local laboratory.

### Concurrent Medical Conditions and Associated Concomitant Medications

Concurrent Medical Conditions	Medication, Dose, Frequency, Route
Hypertension	olmesartan medoxomil, 20 mg, QD, PO (09 Dec 2009
	enalapril, 20 mg, BID, PO, (UK Jun 2008 to 08 Dec 2009)
	verapamil, 80 mg, QD, PO (UK Jun 2009 to 12 Jul 2011)
Hyperlipidemia	pravastatin sodium, 40 mg, QD, PO (UK Jun 2008 to 15 Dec
Asthma	albuterol sulfate, 180 mcg, PRN, INH (UK Nov 2003
	tiotropium bromide, 18 mcg, QD, INH (07 Aug 2009
Cardiac Prophylaxis	aspirin, 81 mg, QD, PO (UK Jun 2008 to 04 Oct 2011)
	fish oil, 1200 mg, QD, PO (UK Jun 2008 to 15 Dec 2011)
Knee Pain	naproxen, 500 mg, PRN, PO (UK Nov 2003 to 12 Jul 2011)
Antidiabetic (Rescue only)	Insulin lispro, 2 IU, AC, SC (04 Oct 2011 to 14 Dec 2011)

**Reviewer Comment:** *Although a relationship to study drug cannot be excluded, the case is confounded by introduction of esomeprazole/naproxen 3 months prior to the event. In addition, details regarding other potential etiologies (HIV, additionally laboratory data ruling out DIC, or TTP) for thrombocytopenia development are lacking, thereby limiting a determination of study drug causality. The diagnosis of drug induced thrombocytopenia is largely made by exclusion of other causes of thrombocytopenia and by correlation of the timing of thrombocytopenia with the administration of an offending medication.*

#### 4MSU (ANEMIA/THROMBOCYTOPENIA EVENTS)

At the 4 month update there was 1 preferred term event of anemia in the all comparators group and 1 event of iron deficiency anemia in the albiglutide arm. There were no additional cases of thrombocytopenia.

#### CUMULATIVE (ANEMIA/THROMBOCYTOPENIA EVENTS)

There were 2 events of anemia and 1 event of iron deficiency anemia in the albiglutide arm compared to 1 event of anemia in all comparators. There was 1 event of thrombocytopenia in the albiglutide arm.

### Acute Myeloid Leukemia (AML)

#### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

Two subjects in the albiglutide arm experienced non-fatal SAEs of acute myeloid leukemia (AML). In addition one subject experienced fatal event of AML in the active comparators grouping (insulin lispro).

Subject 3492754986: A 49-year old male with a history of insomnia, migraines, depression, obesity, hypertension, impotence and basal cell carcinoma of right upper chest was found to have acute myeloid leukemia on study day 328 (41 days after the last dose). The subject also had mild leukopenia since approximately 4 months after starting study drug. He had withdrawn from the study to pursue elective lap band surgery. During the pre-operative period for lap band surgery the subject was found to have hematology abnormalities consistent with **acute myeloid leukemia**. He received chemotherapy (not specified) as treatment for this event. No action was taken with the study medication due to this event as the subject had already withdrawn from treatment.

Subject 7063754993: A 40-year old female without any concurrent or past medical conditions were reported. 250 days after the first dose of albiglutide, the subject experienced Severe acute myeloid leukemia which was considered serious. The subject presented to the emergency room with mucocutaneous bruising and bleeding and was hospitalized. She was diagnosed with **acute myeloid leukemia**, WBC 29.7 (reference range: 3.8 -10.8 Thou/MCL and baseline WBC =7.4). Study medication was withdrawn and she underwent chemotherapy and a bone marrow transplant.

Subject 3101486006: 76 year old female receiving insulin lispro developed AML on study day 219. The narrative lacked information regarding history of malignancy. The subject died from complications related to AML.

***Reviewer Comment: Additional information requested form the applicant revealed that subjects experiencing events of acute myeloid leukemia did not have a history of prior known malignancy at screening. The applicant assumed that there was no prior treatment with chemotherapy or radiotherapy (although it was not reported). There was no history of tobacco use at study entry and information regarding history of Down's syndrome or chemical exposures was not reported.***

## Lymphoma

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

In addition there was one case of lymphoma in the albiglutide arm and 0 in placebo or comparators.

Subject 3545756986: 45 year old male with a past medical history of depression, bronchitis, wheezing, developed **Hodgkin's lymphoma** on study day 398. The study took place in the US.

**Reviewer Comment: Hodgkin's lymphoma has a bimodal age distribution with one peak in young adults (approximately age 20 years) and one in older adults (over age 50 years).<sup>1</sup> The subject does not fall into the age distribution of peak occurrence. However, the narrative lacks information regarding history of EBV virus, HIV status and family history.**

#### 4MSU (AML/LYMPHOMA)

There were no additional cases of acute myeloid leukemia in either arm. One subject in the albiglutide arm developed myelodysplastic syndrome and is described below and one subject in the all comparator group had an event of B cell lymphoma

Subject 3576754988 74-year-old male with hypertension, hyperlipidemia, osteoarthritis and Parkinson's disease had a syncopal episode and was hospitalized. The subject was found to have myelodysplastic syndrome (MDS) on study day 1064.

#### CUMULATIVE (AML/LYMPHOMA)

In the albiglutide group there were 2 subjects with non-fatal events of AML and 1 subject who developed myelodysplastic syndrome (MDS) compared to 1 fatal event of AML in all comparators. One subject had a non-fatal SAE of Hodgkin's lymphoma in the albiglutide group and one subject had a non-fatal event of B cell lymphoma in comparators.

**Reviewer Comment: The incidence of AML increases with age and is more common in adults age 65 and older. The development of AML in the albiglutide clinical program occurred in 2 subjects under age 50 within 1 year of treatment. Hematologic malignancies should be monitored in future studies and pharmacovigilance mechanisms should be utilized post marketing.**

#### RENAL STUDY (GLP114130) NON-FATAL SERIOUS ADVERSE EVENTS

Overall 6% (15/249) of albiglutide treated subjects and 7% (19/246) of sitagliptin treated subjects experienced any SAE (fatal and non-fatal). The majority of SAEs were reported by no more than 2 subjects in both treatment groups, with the exception of atrial fibrillation (4 subjects (1.6%) in the albiglutide group and 1 subject (0.4%) in the sitagliptin group). The incidence of pneumonia was 0.8% (2/249) in the albiglutide treatment group and 1.6% (4/246) in the sitagliptin group. One subject reported necrotizing pneumonia in the albiglutide arm.

Subject 8001130003: 64 year old man with moderate renal impairment (eGFR 34 mL/min) and a history of dyslipidemia and hypertension developed **necrotizing pneumonia** on study day 285. He presented to the hospital with a 10 day history of

cough with sputum and fever requiring hospitalization on study day 285. Upon admission, a chest x-ray revealed right upper lobe consolidation. Sputum cultures grew *Enterobacter*. The primary discharge diagnosis was right upper lobe necrotizing pneumonia. A repeat chest x-ray (unknown date) showed improvement after antibiotic treatment. No action was taken with the study medication.

The applicant notes that in the albiglutide group most SAEs occurred in subjects with mild/moderate renal impairment and there were no SAES in the severe renal impairment category.

All narratives for non-fatal SAEs in the albiglutide program were reviewed. Of note, one subject had a benign pancreatic mass and is described below.

Subject 1494130009: 73 year old man was found to have an incidental pancreatic mass on study day 228. Pathology of the distal pancreas revealed an intraductal papillary mucinous neoplasm, negative for high-grade dysplastic changes, well-differentiated, no invasion demonstrated margins uninvolved by malignancy with mucinous metaplasia present. The mass was diagnosed as a non-cancerous pancreatic mass.

### **7.3.3 Dropouts and/or Discontinuations**

#### **Disposition**

##### **PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)**

Table 37 summarizes overall subject disposition for the P3-ISP. The placebo controlled trials were ongoing at the time of BLA submission and thus there were no subjects who completed active treatment. A greater proportion of subjects in the placebo group discontinued active treatment and a higher number were rescued for hyperglycemia. In all treatment comparison groupings the proportion of overall study drug discontinuations was similar between treatment arms, but adverse event withdrawals (AEWD) were higher in the albiglutide treated subjects.

**Table 37: Overall Subject Disposition by Treatment Group Comparisons (Phase III Integrated Safety Population)**

	Albiglutide vs. All Comparators <sup>1</sup>		Albiglutide vs. Placebo <sup>2</sup>		Albiglutide vs. Active Comparators <sup>3</sup>	
	All Comparators	Albiglutide	Placebo	Albiglutide	Active	Albiglutide
	N=2284 (%)	N=2116 (%)	N=468 (%)	N=923 (%)	N=1816 (%)	N=1766 (%)
Safety population	2284 (100.0)	2116 (100.0)	468 (100.0)	923 (100.0)	1816 (100.0)	1766 (100.0)
Completed active treatment	582 (25.5)	589 (27.8)	0	0	582 (32.0)	589 (33.4)
Discontinued active treatment	659 (28.9)	572 (27.0)	191 (40.8)	301 (32.6)	468 (25.8)	471 (26.7)
Continuing study participation	1043 (45.7)	955 (45.1)	277 (59.2)	622 (67.4)	766 (42.2)	706 (40.0)
Number of subjects rescued	781 (34.2)	704 (33.3)	262 (56.0)	305 (33.0)	519 (28.6)	578 (32.7)
<b>Reason for Discontinuing Active Treatment</b>						
Adverse event	130 (5.7)	164 (7.8)	31 (6.6)	70 (7.6)	99 (5.5)	134 (7.6)
Protocol violation	30 (1.3)	23 (1.1)	7 (1.5)	10 (1.1)	23 (1.3)	19 (1.1)
Noncompliance	65 (2.8)	51 (2.4)	17 (3.6)	25 (2.7)	48 (2.6)	44 (2.5)
Severe or repeated occurrences of hypoglycemia	1 (0.0)	1 (0.0)	0	0	1 (0.1)	1 (0.1)
Lost to follow-up	87 (3.8)	68 (3.2)	23 (4.9)	31 (3.4)	64 (3.5)	54 (3.1)
Subject withdrew consent from active participation	279 (12.2)	219 (10.3)	85 (18.2)	133 (14.4)	194 (10.7)	186 (10.5)
Investigator decided to discontinue study participation	23 (1.0)	17 (0.8)	12 (2.6)	9 (1.0)	11 (0.6)	12 (0.7)
Termination of study by GSK <sup>4</sup>	32 (1.4)	16 (0.8)	10 (2.1)	15 (1.6)	22 (1.2)	10 (0.6)
Other	10 (0.4)	13 (0.6)	6 (1.3)	8 (0.9)	4 (0.2)	11 (0.6)
Missing	2 (0.1)	0	0	0	2 (0.1)	0

Source ISS Table 8, Page 69.

1. Source Data: Table SP3-1.1.1; Phase III Integrated Safety Database (Studies GLP108486, GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, and GLP114179).

2. Source Data: Table SP3-1.1.2; Phase III Integrated Safety Database (Placebo arm studies GLP112753, GLP112755, GLP112756, and GLP112757).

3. Source Data: Table SP3-1.1.3; Phase III Integrated Safety Database (Active comparator arm studies GLP108486, GLP112753, GLP112754, GLP112757, and GLP114179) Note: Final data through Week 104, partial data after Week 104.

4. Includes termination of the study and also termination of selected study sites by GSK.

***Reviewer Comment: Review of line listing discontinuation reasons for the subset of subjects categorized as “other” and “protocol violators” appear to be appropriately coded.***

RENAL STUDY (GLP114130)

As depicted in Table 38, the most common reasons for discontinuing active treatment before week 60 in both groups were adverse events (AEs) and subject withdrawal of consent. The overall incidence of AEWDs was similar between the albiglutide and sitagliptin treated subjects (10.2% vs. 10.3%). AEWDs increased as renal function declined in both arms. However, there were few subjects with severe renal impairment in both treatment groups.

***Reviewer Comment: Interpretation of adverse events in severe renal impairment is limited by the small sample size in both the albiglutide (n=19) and sitagliptin (n=18) treatment groups.***

**Table 38: Subject Disposition: Overall Data Presented by Treatment Group and Renal Impairment Severity (Randomized Population)**

	Albiglutide (N=254) n (%)				Sitagliptin (N=253) n (%)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Randomized Population	130 (100)	105 (100)	19 (100)	254 (100.0)	130 (100)	105 (100)	18 (100)	253 (100.0)
Intent-to-treat Population	126 (96.9)	101 (96.2)	19 (100)	246 (96.9)	124 (95.4)	99 (94.3)	17 (94.4)	240 (94.9)
Received at least 1 treatment dose (Safety Population)	128 (98.5)	102 (97.1)	19 (100)	249 (98.0)	128 (98.5)	101 (96.2)	17 (94.4)	246 (97.2)
Completed active treatment	107 (82.3)	76 (72.4)	15 (78.9)	198 (78.0)	107 (82.3)	61 (58.1)	10 (55.6)	178 (70.4)
Discontinued active treatment	21 (16.2)	26 (24.8)	4 (21.1)	51 (20.1)	21 (16.2)	40 (38.1)	7 (38.9)	68 (26.9)
Reason for discontinuing active treatment								
Adverse event	6 (4.6)	17 (16.2)	3 (15.8)	26 (10.2)	4 (3.1)	15 (14.3)	7 (38.9)	26 (10.3)
Protocol violation	0	1 (1.0)	0	1 (0.4)	0	4 (3.8)	0	4 (1.6)
Noncompliance	3 (2.3)	0	0	3 (1.2)	3 (2.3)	2 (1.9)	0	5 (2.0)
Severe or repeated occurrences of hypoglycemia				0				0
Lost to follow-up	2 (1.5)	1 (1.0)	1 (5.3)	4 (1.6)	3 (2.3)	1 (1.0)	0	4 (1.6)
Subject withdrew consent from active participation	8 (6.2)	4 (3.8)	0	12 (4.7)	11 (8.5)	15 (14.3)	0	26 (10.3)
Investigator decided to discontinue participation	2 (1.5)	3 (2.9)	0	5 (2.0)	0	3 (2.9)	0	3 (1.2)

Source Data: CSR GLP114130 Table 5 page 77. Note: Percentages were calculated using the number of subjects randomly assigned within each subgroup as the denominator.

## Adverse Event Withdrawals

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

#### Albiglutide vs. Placebo

As depicted in Table 39, a higher incidence of any AE leading to withdrawal of treatment occurred in albiglutide treated subjects compared to placebo (7.5 vs. 6.6%, respectively). This imbalance was primarily driven by events of injection site reactions (2.1% vs. 0.4%) and injection site rash (0.3 % vs. 0). There were numerically more AE withdrawals in the albiglutide group for pancreatitis, liver enzyme abnormalities and hypoglycemia (0.2% vs. 0). Gastrointestinal events were balanced overall except for a higher proportion of vomiting events (0.2% vs. 0 in placebo) leading to withdrawal in albiglutide treated subjects.

**Table 39: P3-ISP: AE leading to withdrawal of active treatment occurring in at least 2 Subjects in either treatment group (P3- ISP Albiglutide vs.Placebo)**

System Organ Class AE Preferred Term		
	Placebo (N=468)	Albiglutide (N=923)
	n (%)	n (%)
<b>Any AE leading to withdrawal of active treatment</b>	31 (6.6)	69 (7.5)
<b>General disorders and administration site conditions</b>	2 (0.4)	19 (2.1)
Injection site reaction	0	11 (1.2)
Injection site rash	0	3 (0.3)
<b>Gastrointestinal disorders</b>	8 (1.7)	16 (1.7)
Diarrhea	3 (0.6)	4 (0.4)
Nausea	2 (0.4)	3 (0.3)
Pancreatitis	0	2 (0.2)
Vomiting	0	2 (0.2)
<b>Cardiac disorders</b>	4 (0.9)	6 (0.7)
<b>Investigations</b>	2 (0.4)	6 (0.7)
Alanine aminotransferase increased	0	2 (0.2)
Liver function test abnormal	0	2 (0.2)
<b>Neoplasms benign, malignant and unspecified (including cysts and</b>	4 (0.9)	5 (0.5)
<b>Skin and subcutaneous tissue disorders</b>	2 (0.4)	4 (0.4)
Urticaria	2 (0.4)	0
<b>Infections and infestations</b>	1 (0.2)	3 (0.3)

<b>Metabolism and nutrition disorders</b>	1 (0.2)	3 (0.3)
Hypoglycemia	0	2 (0.2)
<b>Nervous system disorders</b>	3 (0.6)	3 (0.3)
<b>Musculoskeletal and connective tissue disorders</b>	3 (0.6)	1 (0.1)

For each level of summarization, a subject was counted once if the subject reported 1 or more events  
Source: ISS Table 91 page 269.

### Albiglutide vs. All Comparators

In the albiglutide group there was a greater proportion of any AEs leading to withdrawal (AEWD) of active treatment compared to (7.5 vs. 5.7%) all comparators (See Table 40). This imbalance was primarily driven by withdrawals due to injection site reactions. In the Gastrointestinal (GI) Disorders SOC, the proportion of subjects with events leading to withdrawal was the same (1.8%) in each group, with nausea being the most common GI event leading to withdrawal (0.5% in both groups). There were more withdrawals from treatment in the albiglutide arm for vomiting (0.4 vs. 0.2 %).

**Table 40: P3-ISP: On-Therapy Adverse Events Leading to Withdrawal of Active Treatment occurring in at Least 0.2% of Subjects in Either Treatment Group. – Albiglutide Versus All Comparators**

System Organ Class AE Preferred Term	All Comparators (N=2284)	Albiglutide (N=2116)
	n (%)	n (%)
Any AE leading to withdrawal of active treatment	130 (5.7)	159 (7.5)
<b>General disorders and administration site conditions</b>	13 (0.6)	44 (2.1)
Injection site reaction	0	31 (1.5)
Injection site rash	0	4 (0.2)
<b>Gastrointestinal disorders</b>	41 (1.8)	39 (1.8)
Nausea	12 (0.5)	11 (0.5)
Vomiting	5 (0.2)	8 (0.4)
Diarrhea	8 (0.4)	6 (0.3)
Abdominal pain	5 (0.2)	2 (0.1)
<b>Investigations</b>	13 (0.6)	14 (0.7)
Alanine aminotransferase increased	0	4 (0.2)
<b>Cardiac disorders</b>	9 (0.4)	13 (0.6)
Myocardial infarction	0	4 (0.2)

Source Data: SCS Table 35 page AE = adverse event; SOC = system organ class.

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

Although not depicted in Table 16 there were slightly higher rates of withdrawals in the albiglutide arm vs. comparators in the SOC for infections (0.3%, 7/2116 vs. 0.1%, 2/2284, respectively) and skin disorders (0.3%, 7/2116 vs. 0.2%, 4/2284) SOC. These were primarily single events, and review of case narratives did not identify a new safety concern. In addition narratives for preferred term events of abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort and projectile vomiting did not suggest an additional safety finding. However, in many cases there was an overall lack of information to determine the cause for withdrawal.

When combining preferred terms of pancreatitis, acute pancreatitis and viral pancreatitis, 5 subjects withdrew in the albiglutide group vs. 2 in all comparators. One subject in the albiglutide group withdrew for drug induced liver injury, and one subject in each group withdrew for hypersensitivity. Withdrawals for elevated ALT levels were higher in the albiglutide group and a slightly higher number of subjects treated with albiglutide withdrew for CV events. Cases of pancreatitis, liver, cardiovascular, gastrointestinal, injection site and hypersensitivity events are discussed separately.

#### 4MSU ADVERSE EVENT WITHDRAWALS

In the albiglutide group 0.8%, 11/1427 subjects withdrew vs. 1.1%, 17/1595 in all comparators. Events in the Cardiac Disorders SOC were the most frequently reported reason for withdrawal in both groups, (0.1%, 2/1427) albiglutide treated vs. (0.2% 3/1595) comparators.

#### CUMULATIVE ADVERSE EVENT WITHDRAWALS

Across the P3-ISP, 170 subjects (8.0%, 170/2116) in the albiglutide treatment group and 145 subjects (6.3%, 145/2284) in the all comparators treatment group had an on-therapy AE that led to study drug withdrawal. The proportion of subjects with AEWs within each SOC was generally balanced across the 2 treatment groups except for the General disorders SOC. In the albiglutide group, events in the General disorders and Administration Site Conditions SOC were the most frequently reported events leading to withdrawal of active treatment (2.2 %, 46/2116 vs. 0.6% 13/2284 in comparators). This imbalance was driven by injection site reactions (1.5% 31/2116 vs. 0 in comparators).

#### RENAL STUDY (GLP114130) ADVERSE EVENT WITHDRAWALS

The incidence of AEs leading to withdrawal of active treatment was approximately 10% in both treatment groups (Table 41). Renal and urinary events were the most frequent reported events in both groups with an overall higher proportion in the sitagliptin arm. Four subjects in the albiglutide group and 1 subject in the sitagliptin group experienced single gastrointestinal events leading to withdrawal of active treatment.

**Table 41: GLP114130: On-Therapy Adverse Events Leading to Withdrawal of Active Treatment: Overall Data (Safety Population)**

System Organ Class Preferred Term		
	Sitagliptin (N=246)	Albiglutide (N=249)
	n (%)	n (%)
Any event	26 (10.6)	26
<b>Renal and urinary disorders</b>		
Any event	13 (5.3)	10 (4.0)
Renal failure	9 (3.7)	3
Renal impairment	3 (1.2)	5
Calculus urinary	1 (0.4)	0
Nephropathy	0	1
Renal failure chronic	0	1
<b>Gastrointestinal disorders</b>		
Any event	1 (0.4)	4
Nausea	1 (0.4)	1
Diarrhea	0	1
Gastrointestinal disorder	0	1
Pancreatitis	1 (0.4)	1

Source CSR GLP114130 Table 53, Page 170

### 7.3.4 Significant Adverse Events

Significant adverse events are discussed under non-fatal serious adverse events in Section 7.3.2.

### 7.3.5 Submission Specific Primary Safety Concerns

#### THYROID ADVERSE EVENTS

Standard MedDRA query identified thyroid adverse events revealed a similar incidence between albiglutide (1.7%) and all comparators (1.9%), and a slightly higher incidence in albiglutide treated subjects (2.1%) compared to placebo (1.7%). Overall there were 5 cases of thyroid cancer in the clinical program (2 albiglutide subjects and 2 comparators and 1 placebo). In the albiglutide arm there was 1 case of on-therapy papillary thyroid cancer and 1 case of medullary thyroid cancer (coded as post therapy and likely not drug related). Although the available data does not suggest a thyroid cancer safety signal, it should be noted that numerous cases of anatomic thyroid abnormalities were

not followed up by biopsy or imaging. Therefore determination of risk and causality is limited by lack of sufficient information.

Nonclinical rodent studies suggest that GLP-1 receptor agonists may be associated with an increased risk of thyroid C-cell hyperplasia and C-cell tumors. Medullary thyroid cancer (MTC) is a neuroendocrine tumor of the parafollicular or C cells of the thyroid gland. As a result of the preclinical cancer findings with other GLP-1 agonists, thyroid tumors were adverse events of special interest in the albiglutide clinical program. Of note, preclinical carcinogenicity studies have not been conducted with albiglutide due to the development of drug clearing, anti-drug antibody development in rodents.

Thyroid related adverse events and SAEs were flagged by the investigator in the AE electronic case report form (eCRF). If a thyroid nodule was detected at screening or during the study it was further evaluated as deemed clinically appropriate (ultrasound of the neck or fine needle aspiration). In addition to investigator identified thyroid events, a customized MedDRA query was conducted to identify thyroid-related terms.

***Reviewer Comment: An information request was sent to the sponsor for clarification of how thyroid events and in particular thyroid nodules were identified and screened for in the clinical program. The applicant was asked to describe the internal safety monitoring process which was triggered when one such event was identified and to clarify whether the process was prospective or retrospective. The applicant clarified that thyroid-related assessments performed at screening included a thyroid examination (i.e., palpation of the thyroid gland), thyroid-stimulating hormone assessment, and formal review of general and thyroid-specific past medical history. If a thyroid nodule was detected investigators were instructed to further evaluate in view of clinical management guidance published in US and Europe. However, protocols did not mandate these specific guidelines be followed exclusively. Therefore, medical judgment of the investigators and medical practice in the different countries of the global program was respected. The data were also regularly reviewed by the Independent Data Monitoring Committee (IDMC).***

#### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

##### Albiglutide vs. Placebo

Compared to placebo (see Table 42), a greater number of subjects treated with albiglutide experienced thyroid related events (2.1% albiglutide vs. 1.7% placebo). This imbalance was primarily drive by events of goiter and hypothyroidism. One case of thyroid cancer occurred in both albiglutide and placebo treated subjects.

**Table 42: P3-ISP On-therapy Thyroid Adverse Events Identified by MedDRA Query with at least 1 event in the albiglutide group (Albiglutide vs. Placebo)**

<b>System Organ Class SOC</b>	Placebo N=468	Albiglutide N=923
	n (%)	n (%)
<b>Any Event</b>	8 (1.7)	19 (2.1)
<b>Endocrine disorders</b>		
Any Event	4 (0.9)	14 (1.5)
Goiter	0	6(0.7)
Hypothyroidism	2 (0.4)	6 (0.7)
Hyperparathyroidism	0	1 (0.1)
Sec. Hyperparathyroidism <sup>#</sup>	0	1(0.1)
Hyperthyroidism	1(0.2)	1(0.1)
<b>Neoplasms*</b>		
Any Event	3 (0.6)	4(0.4)
Thyroid neoplasm	2 (0.4)	4(0.4)
Thyroid cancer	1(0.2)	1(0.1)
<b>Investigations</b>		
Any Event	1(0.2)	3 (0.3)
Increased blood calcitonin	1 (0.2)	3 (0.3)
<b>Metabolism and Nutrition</b>		
Any event	0	1 (0.1)
Hypercalcitonemia	0	1 (0.1)

Modified from ISS Table SP3-28.4.2 page 12051.

\* Neoplasms = benign, malignant and unspecified (including cysts and polyps).

<sup>#</sup> Sec. = Secondary hyperparathyroidism.

### Albiglutide vs. All Comparators

As detailed in Table 43, thyroid adverse events were balanced between albiglutide (1.7%) and all comparators (1.9%). A higher number of goiter events occurred in albiglutide treated subjects compared with all comparators subjects (0.6% vs. 0.3%, respectively). Thyroid-related neoplasms (neoplasm, cancer, and adenoma) occurred less frequently in the albiglutide group (0.4%) vs. all comparators (0.6%). One subject treated with albiglutide had an event of thyroid cancer compared to 3 cases in all comparators.

**Table 43: P3-ISP -On-therapy Thyroid Adverse Events Identified by MedDRA Query with at least one event in the albiglutide group (Albiglutide versus All Comparators)**

	All Comparators N =2284	Albiglutide N=2116
	n (%)	n (%)
<b>Any Event</b>	43 (1.9)	37 (1.7)
<b>Endocrine disorders</b>		
Any Event	23 (1.0)	27 (1.3)
Goiter	6	12 (0.6)
Hypothyroidism	11 (0.5)	11 (0.5)
Hyperparathyroidism	0	1
Prim. Hyperparathyroidism	0	1
Sec. Hyperparathyroidism	0	1
Hyperthyroidism	2 (0.1)	1
Thyroid cyst	0	1
<b>Neoplasms*</b>		
Any Event	14 (0.6)	8
Thyroid neoplasm	10 (0.4)	8
Thyroid cancer	3	1
<b>Investigations</b>		
Any Event	11 (0.5)	7
Blood calcitonin increased	10 (0.4)	6
Blood parathyroid hormone increased	0	1
<b>Congenital, familial and</b>		
Any Event	0	1
Multiple endocrine adenomatosis Type II	0	1
<b>Metabolism and nutrition</b>		
Any Event	0	1
Hypercalcaemia	0	1

Modified from ISS table 121 pg 391. 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.

Neoplasms = benign, malignant and unspecified (including cysts and polyps).

Prim.= Primary hyperparathyroidism, Sec.= secondary hyperparathyroidism.

## Anatomic Thyroid Abnormalities

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

The sponsor reviewed the database for potential anatomic abnormalities identified by the investigator and MedDRA query (search terms: thyroid neoplasm, thyroid adenoma, thyroid cyst, thyroid cancer, thyroid mass, thyroiditis, and goiter).

- 40 unique subjects with anatomic thyroid abnormalities were identified and are described in Table 44. The number of subjects with thyroid nodules or potential thyroid nodules was low and balanced across all treatment groups.

- 4/40 subjects had confirmed on-therapy thyroid cancers (1 albiglutide subject, 1 placebo subject, and 2 active comparator subjects). There were 3 cases of papillary thyroid carcinoma (1 albiglutide subject vs. 2 all comparators) and 1 case of medullary thyroid cancer (1 placebo subject).
- In addition, 1 case of medullary thyroid cancer in the albiglutide group was confirmed during the post-therapy period.
- 33/40 subjects (17 albiglutide-treated subjects and 16 comparators) had “other” cases of interest (i.e., non-diagnostic fine needle aspiration, no biopsy performed, or unavailable information on the thyroid-specific eCRFs). These subjects are described in Table 44.

**Table 44: P3- ISP Description of anatomic thyroid abnormalities**

	All Comparators 2284	Albiglutide 2116
<b># of subjects with nodules or potential nodules</b>	21	19
Confirmed thyroid cancer	3	2
Confirmed non – malignant neoplasm	2	0
<b>Others</b>	16	17
Thyroid Neoplasm not biopsied	9	4
Non diagnostic biopsy result	0	2
Goiter	1	6
Thyroid cyst	0	1
Thyroid adenoma	1	0
Thyroiditis	1	0
No eCRF/narrative*	4	4

Reviewer generated.

\* For these subjects, the medical history, AE verbatim terms, and calcitonin values were reviewed. The anatomic thyroid abnormality reported for all of these subjects was associated with the AE preferred term of goiter, and all calcitonin values during the study were <0.58 pmol/L (<2 pg/mL).

### Confirmed Thyroid Cancer Cases

#### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

There were 2 cases of confirmed thyroid cancer in the albiglutide group vs. 3 in all comparators.

#### On-therapy

Subject 3487753983: 76-year-old woman was found to have a right lobe thyroid nodularity on baseline physical exam. The subject’s baseline calcitonin value (taken

from a biomarker sample) was normal (<2 pg/mL). Ultrasonography revealed 2 complex cystic nodules in the right mid pole of the thyroid. There was no treatment reported and study drug was continued. On study day 243 the subject was diagnosed with **papillary thyroid cancer** and underwent total thyroidectomy.

### Post-Therapy

Subject 1043486004: 45-year old female was found to have an elevated baseline calcitonin value (480 pg/mL (nml < 5pg/ml)) on study day 4. The subject was diagnosed with pheochromocytoma and genetic screening revealed the presence of the RET proto-oncogene mutation associated with MEN2. The subject was withdrawn from the study approximately 21 days after receiving the first dose of albiglutide. The subject underwent a total thyroidectomy and was diagnosed with **medullary thyroid cancer** with pathology confirmed diagnosis of papillary, medullary and metastatic, malignant thyroid cancer on study day 101.

***Reviewer Comment: The development of medullary thyroid cancer in this subject is the result of a genetic mutation in the RET gene and not likely related to study drug.***

### **Non- biopsied or non –diagnostic thyroid nodules**

Summary of 6 albiglutide treated subjects with either non-biopsied thyroid neoplasms (n=4) or non-diagnostic thyroid nodules (n=2) were reviewed and are briefly described below.

Subject 3626757987: 63 year old male was found to have a solitary nodule in the left lower lobe measuring 2.7 x 2.4 centimeters on study day 368. Thyroid stimulating hormone was normal and pathology was suggestive of inflamed colloid nodule/ thyroiditis. The case was categorized as **non-diagnostic**.

Subject 0666753986: 69-year old male was found to have a 0.6 x 0.5 cm nodule (fine needle aspirate result was **non-diagnostic**) on study day 574. No action was taken with the study medication and treatment was not reported

### Non- biopsied anatomic abnormalities

Subject 3769757980: 54-year old female was found to have multiple sub-centimeter thyroid nodules bilaterally with increased vascularity on study day 797. No action was taken with the study medication and treatment for the nodules was not reported.

Subject 3576754987: 66-year old female was found to have a solitary nodule of the left upper lobe (dimensions not provided) on study day 819. No action was taken with the study medication and treatment was not reported.

Subject 3604754986: 82-year old female was found to have a multinodular neoplasm measuring 2.8 x 2.4 cm and located in the right upper lobe on study day 812. Results of thyroid ultrasound were not provided. Additional treatment was not reported.

Subject 1030179005: 55-year old female was found to have a nodule 14 days after the 32nd dose of albiglutide that was located in the right upper lobe measuring 1 x 1 cm. An ultrasound was performed (results not reported). Results from thyroid function tests were normal.

***Reviewer Comment: The majority of subjects in the clinical program identified to have thyroid nodules either had non-diagnostic fine needle aspirations, did not undergo biopsy, or had insufficient information collected on the thyroid-specific eCRFs. The sponsor was asked to provide updated data on these cases clarifying why a definitive diagnosis was not established. The applicant stated that the study protocols did not require the investigator to establish a definitive diagnosis for every thyroid event reported and investigators were instructed to further evaluate thyroid nodules as appropriate. Medical practices in the different countries of the global program were respected and specific instruction on patient management was not mandated by protocols. Biopsy of thyroid nodules was left to the medical judgment of the investigator. Due to the lack of standardization in the approach to thyroid nodules in the clinical program there is a paucity of information regarding anatomic thyroid abnormalities identified in subjects treated with albiglutide, making an assessment of thyroid cancer development inconclusive. Similar to other GLP1 agonists, this reviewer recommends that the product label describe the risk of medullary thyroid cancer (MTC) with GLP use in animal models and thyroid cancer continue to be monitored in future studies with a standardized approach to the development of new nodules.***

#### 4MSU ANATOMIC THYROID ABNORMALITIES

During the timeframe for the safety update 7 subjects had new thyroid nodules identified by investigators and MedRA query (4 subjects in the albiglutide group and 3 subjects in the all comparators group). Albiglutide treated subjects with new thyroid anatomic abnormalities are further described below.

- Subject 3757754986: 51 year old female with a left upper lobe nodule identified on study day 824. The FNA was benign.
- Subject 3677754987: 54 year old male found to have a thyroglossal cyst on study day 1093.

- Subject 7063754986: 72 year old male found to have a diffuse thyroid goiter on study day 1093.
- Subject 37617549187 was a 54 year old female, who was found to have multiple thyroid nodules 1095 days after the study began. Calcitonin levels were < 2pg/ml at baseline and at weeks 52, 104, and 156. Additional data was not provided.

## CUMULATIVE ANATOMIC THYROID ABNORMALITIES

The incidence of cumulative thyroid adverse events identified by MedDRA query were balanced between the albiglutide (2%, 42/2116 subject with 55 events) and all comparators groups (2.2%, 50/2284 with 60 events. A total of 48 unique subjects were identified with anatomic abnormalities or potential anatomic abnormalities of the thyroid gland (7 new cases identified during the safety update and 40 cases at the time of the original BLA). One additional subject had an AE of hypothyroidism reported in the original BLA submission, but the investigator had not completed the thyroid nodule eCRF.

These 48 unique subjects are classified as follows:

- 5 subjects with confirmed thyroid cancers (2 albiglutide vs. 3 comparators).
- 3 subjects with confirmed nonmalignant neoplasms
- 40 subjects with other cases of interest (i.e., non-diagnostic fine needle aspiration or no biopsy performed)

## Calcitonin Measurements

Calcitonin is secreted mainly by parafollicular C cells and elevated serum levels (>100 pg/mL) may be suggestive of medullary thyroid carcinoma. Clinically calcitonin measurements are generally utilized in the evaluation of tumor size and progression, and as a metric of biochemical improvement of medullary thyroid carcinomas. However, due to the fact that GLP-1 agonists were believed to stimulate calcitonin release and result in c-cell hyperplasia, levels were monitored throughout the albiglutide clinical program.

## PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

Overall, there did not appear to be clinically relevant changes from baseline in calcitonin measurements.

- In the P3-ISP the applicant defined clinically concerning calcitonin values as >29.2 pmol/L (100 pg/mL).
- A protocol amendment applied to all Phase III studies (except GLP108486 and GLP114179) added a measurement of calcitonin at baseline and annually throughout the study. Any subject found to have a baseline calcitonin value of >29.2 pmol/L (100 pg/mL) at Week -1 was discontinued from the study and

underwent further evaluation. Subjects who had already passed the baseline assessment at the time of the protocol amendment did not have a baseline calcitonin measurement or sample drawn. Each of these subjects had a stored baseline serum sample that had been collected for future measurement

- In study GLP108486 calcitonin measurements were conducted at baseline, week 26 and week 52.
- In study GLP114179, measurements for serum calcitonin were conducted at baseline and week 32.

**Reviewer Comment: The applicant was asked to clarify whether baseline calcitonin levels were drawn in all subjects after implementation of the protocol amendment. The applicant states that for subjects enrolled in studies prior to protocol amendment 1 baseline calcitonin was retrospectively measured using an aliquot from a stored baseline serum sample. Overall, across the five 3-year studies, approximately 1722 subjects were randomized after amendment 1 and 1346 (78%) had a baseline calcitonin value.**

Albiglutide vs. Placebo:

Clinically concerning values:

There were 4 subjects with calcitonin values of clinical concern ( $>29.2$  pmol/L (100 pg/mL)) at any on-therapy visit (3/379 subjects in the placebo group and 1/803 subjects in the albiglutide group). However, all 4 subjects had elevated calcitonin values at baseline.

Shifts from baseline:

Calcitonin shifts from baseline ( $>2\times$ ULN) involved 9 subjects (1 subject in the albiglutide group (described below) and 8 subjects in the all comparators group).

Subject 3617754986: 60 year old male with a history of cardiomyopathy and dyslipidemia had a normal baseline calcitonin value of 1.46 pmol/L (normal range:  $<3.2$  pmol/L). At week 52 the subject's calcitonin value increased to 2.04 pmol/L and at week 117 (study day 813) it had risen to 12.85 pmol/L. The subject also developed hypothyroidism on study day 242.

**Reviewer Comment: Chronic autoimmune thyroiditis has been associated with elevated calcitonin levels. It is unclear if the subject had Hashimoto's disease which is a common cause of hypothyroidism. In addition the subject's medication history is unknown. Prolonged treatment with omeprazole ( $> 2$  to 4 months), beta-blockers, and glucocorticoids have been associated with hypercalcitoninemia.**

### Albiglutide vs. All Comparators

Clinically concerning values:

7 subjects (3/1868 subjects in the albiglutide group and 4/2015 subjects in the all comparators group) had calcitonin values of clinical concern (>29.2 pmol/L) at any on-therapy visit.

Subject 1043486004 had undiagnosed MEN-2A, baseline elevation of calcitonin and medullary thyroid cancer – see narrative above

Subject 1149486002: 54-year-old female had a baseline calcitonin of 28.6 pmol/L which increased to 45.6 pmol/L at week 26 and 39. No additional diagnostic tests or thyroid events were recorded. A full narrative was not provided.

***Reviewer Comment: Follow-up information was requested from the applicant. The sponsor notes that the study medical monitor queried the site for any additional follow-up information related to this case. Although thyroid ultrasonography was not performed, a thyroid CT scan (without contrast) and a nuclear medicine thyroid imaging study (with iodine uptake) were performed. Thyroid biopsy of a right mid pole nodule included the differential diagnoses between a follicular adenoma and a hyperplastic adenomatous nodule/goiter with focal microfollicular pattern. Of note, the pathologist favored the latter diagnosis. The clinical relevance of the microfollicular pattern is not clear from the additional information provided.***

Subject 5779755983: 72-year-old female with a history of hypertension and peripheral vascular disease had a baseline calcitonin obtained from a frozen specimen that was 113.30 pmol/L. Her calcitonin value at week 52 was <0.58 pmol/L and the value at week 104 was 190.68 pmol/L. Thyroid ultrasonography was normal without any nodules. The subject was withdrawn from the study and repeat calcitonin values (around week 108) were 162.94 pmol/L and 137.53 pmol/L, respectively

***Reviewer Comment: Review of the narrative revealed that the subject was on omeprazole for several years which can result in hypercalcitonemia. However calcitonin levels > 29.6 pmol/ml are concerning for MTC and the thyroid ultrasound report was requested and reported as normal without anatomic abnormalities.***

The sponsor also evaluated subjects with calcitonin level > 14.6pmol/L (50 pg/ml). Three albiglutide cases and 5 cases in the all comparators group were identified. Clinical summary review for albiglutide treated subjects 3601757995, 1075486044, and 3440757988 revealed no additional thyroid related events in these subjects.

Shifts from baseline:

Shifts in calcitonin from normal to abnormal values were small for both treatment groups (3.3% in the albiglutide group and 3.6% in the all comparators) from baseline to week 104. For the majority of subjects, abnormal values did not approach 2x ULN (14.6 pmol/L [50 pg/mL]).

#### 4MSU CALCITONIN MEASUREMENTS

There were no new subjects with a calcitonin value of clinical concern >29.2 pmol/L (> 100 pg/ml). One new subject in the albiglutide group had a calcitonin measurement  $\geq$ 14.6 pmol/L (50 pg/mL)

Subject 3423757986: 46 year old male had an elevated calcitonin measurement of 57 pg/mL at week 156 (end of treatment). This subject also had elevated calcitonin measurements at baseline (40 pg/mL), week 52 (41 pg/mL), and week 104 (48 pg/mL). The subject reported 1 thyroid-related AE of hypothyroidism within the first 104 weeks of study treatment. Additional details regarding medication history and nature of thyroid disease were not provided.

#### RENAL STUDY (GLP114130) THYROID ADVERSE EVENTS

In T2DM subjects with mild, moderate, and severe renal impairment and anatomic thyroid abnormalities, there were no confirmed cases of thyroid cancer (6 albiglutide-treated subjects and 2 sitagliptin-treated subjects had thyroid nodules). Both albiglutide subjects had confirmed non-malignant neoplasms.

Brief narratives for albiglutide treated subjects with nodules are described below.

Subject 1171130002: 56-year old female with a history of thyroid nodules was found on study day 84 to have an increase in size of a left sided nodule from years prior. The subject had a left hemithyroidectomy and no malignancy was identified. An additional cystic nodule on the right side measuring 3.4 cm was noted on study day 160 and did not have a biopsy reported.

Subject 8311130004: 56-year old Asian male was found to have a thyroid nodule on study day 308 which was biopsied and determined to be benign.

Subject 1486130009: 61-year old female, on study day 367 the subject was found to have a solitary thyroid nodule in the left upper lobe measuring 1 x 1 cm. There was no biopsy reported. The subject had an ultrasound (results not provided).

Subject 1474130006: 56-year old male with a history of hypothyroidism and unknown thyroid nodule was found on study day 364 to have a thyroid nodule that was determine

to be not clinically significant by the investigator. Additional information was not provided in the narrative (TSH 4.5 (nml 0.5 -5.5 MU/L)).

Subject 1206130001: 80-year old male was found on study 18 to have a right lower lobe solitary nodule measured 0.6 x 0.6 cm. No further action was taken.

Subject 1204130002: 49 year old found to have an enlarged thyroid. A narrative was not provided.

***Reviewer Comment: The overall lack of information regarding the anatomic abnormalities limits interpretation of a relationship to study drug.***

There were no adverse events of abnormal calcitonin values reported in the renal study.

## **LIVER SAFETY ANALYSES**

Overall liver related adverse events were similar between albiglutide and all comparators. (3.9% and 4%, respectively). The greatest imbalance not in favor of albiglutide was observed for events of GGT elevations (1.2%, 26/2116 vs. 0.7%, 15/2284). Two subjects in the albiglutide arm met biochemical criteria for Hy's Law. One case occurred in a subject with Hepatitis B and the other case was suggestive of drug induced hepatocellular injury but was confounded by the presence of gallstones. Many events of hepatocellular injury in the albiglutide arm occurred in subjects with underlying cholestasis. This relationship between GGT elevations, cholestasis and liver injury has not been fully elucidated and should be monitored in future studies.

### **PHASE 3-INTEGRATED SAFETY POPULATION (P3-ISP)**

In the liver safety analysis the sponsor evaluated adverse events from the Hepatobiliary Disorders and Investigations SOC (liver-related only) in conjunction with listings of subjects for whom the liver event eCRFs were completed along with laboratory data (liver function tests (LFTs) of clinical concern).

Subjects were excluded in the P3-ISP if they met the following criteria:

- History of total bilirubin  $>1.5 \times \text{ULN}$  (unless the subject had a known history of Gilbert's syndrome and a fractionated bilirubin that showed conjugated bilirubin  $<35\%$  of total bilirubin)
- ALT or AST  $>2.5 \times \text{ULN}$

The protocols of all the studies comprising the P3-ISP defined stopping criteria and follow-up for subjects with elevated LFT results as follows:

1. ALT  $\geq 3 \times \text{ULN}$  and bilirubin  $\geq 2 \times \text{ULN}$  ( $>35\%$  direct bilirubin) and/or international normalized ratio  $>1.5$  (serum bilirubin fractionation was performed if testing was

available. If testing was unavailable, presence of detectable urinary bilirubin on dipstick was recorded, indicating direct bilirubin elevations and suggesting liver injury)

2. ALT  $\geq 8 \times$ ULN
3. ALT  $\geq 5 \times$ ULN but  $< 8 \times$ ULN persists for  $\geq 2$  weeks
4. ALT  $\geq 3 \times$ ULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
5. ALT  $\geq 5 \times$ ULN but  $< 8 \times$ ULN and could not be monitored weekly for  $\geq 2$  weeks

### All Hepatobiliary Adverses Events

#### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

##### Albiglutide vs. Placebo

The proportion of subjects experiencing an adverse event in the hepatobiliary and investigation disorders SOCs were similar between albiglutide and placebo treated subjects. As detailed in Table 45, there were more subjects treated with albiglutide who experienced an adverse events of increased GGT when compared to placebo treated subjects (1.5% vs. 0.9%, respectively) and increased hepatic enzymes (1.1% vs. 0.6%, respectively).

**Table 45: P3-ISP: On-therapy Adverse Events by High Level Term in Hepatobiliary Disorders SOC and Investigations SOC with a higher % in in the albiglutide group - Albiglutide vs.Placebo**

<b>SOC</b> <b>High Level Term</b> Preferred Term	Placebo (N=468)	Albiglutide (N=923)
	n (%)	n (%)
<b>Hepatobiliary disorders SOC</b>		
Any event	8 (1.7)	14 (1.5)
<b><i>Cholecystitis and cholelithiasis</i></b>	3 (0.6)	6 (0.7)
Cholecystitis	0	3 (0.3)
Cholelithiasis	3 (0.6)	3 (0.3)
Cholecystitis acute	1 (0.2)	0
Hepatomegaly	0	2 (0.2)
<b>Investigations SOC</b>		
Any event	48 (10.3)	102 (11.1)
<b><i>Liver function analyses</i></b>	12 (2.6)	32 (3.5)
GGT increased	4 (0.9)	14 (1.5)
Hepatic enzyme increased	3 (0.6)	10 (1.1)
ALT increased	3 (0.6)	6 (0.7)

AST increased	2 (0.4)	5 (0.5)
Liver function test abnormal	1 (0.2)	4 (0.4)

Source Modified from ISS Table 198, Page 597. AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; For each level of summarization, a subject was counted once if the subject reported 1 or more events.

### Albiglutide vs. All Comparators

Overall on-therapy AEs in High Level Term were similar between treatment groupings (Table 46). There was an imbalance in the proportion of subjects experiencing elevated GGT levels not in favor of the albiglutide group. In addition 1 subject in the albiglutide group had an event coded as “drug induced liver injury”.

**Table 46: P3-ISP: On-therapy Adverse Events by High Level Term in Hepatobiliary Disorders SOC and Investigations SOC - Albiglutide vs. All Comparators**

SOC <i>High Level Term</i> Preferred Term	All Comparators	Albiglutide
	(N=2284)	(N=2116)
<b>Hepatobiliary disorders SOC</b>	<b>n (%)</b>	<b>n (%)</b>
Any event	34 (1.5)	28 (1.3)
<b><i>Cholecystitis and cholelithiasis</i></b>	16 (0.7)	13 (0.6)
Cholelithiasis	11 (0.5)	7 (0.3)
Cholecystitis	1(0)	5 (0.2)
Cholecystitis Chronic	0	1 (0)
Cholecystitis acute	5 (0.2)	0
<b><i>Hepatocellular damage and hepatitis NEC</i></b>	11 (0.5)	11 (0.5)
Hepatic steatosis	10 (0.4)	11 (0.5)
Drug-induced liver injury	0	1 (0.0)
<b><i>Hepatobiliary signs and symptoms</i></b>	3 (0.1)	4 (0.2)
Hepatomegaly	2 (0.1)	4 (0.2)
Gallbladder disorders NEC	0	1 (0.0)
Biliary dyskinesia	0	1 (0.0)
<b>Investigations SOC</b>		
Any event	269 (11.8)	228 (10.8)

<b><i>Liver function analyses</i></b>	47 (2.1)	48 (2.3)
GGT increased	14 (0.6)	24 (1.1)
ALT increased	14 (0.6)	15 (0.7)

Source Data: Table 197, Page 594. AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; N/A = not applicable; NEC = not elsewhere classified; SOC = System Organ Class. Note: On-therapy events are those that had a start date on or after the first day of study medication and within 56 days

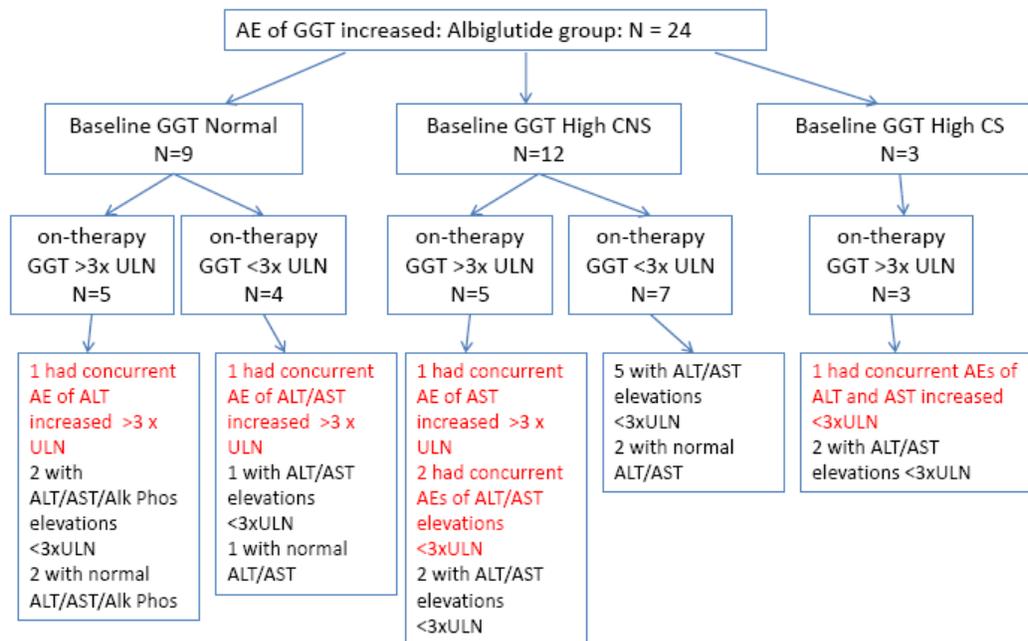
### **Cases Coded to the Adverse Event Term “GGT increased”**

#### **PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)**

As described above an imbalance not in favor of albiglutide was noted for GGT elevations in both the placebo and all comparators treatment comparison groupings. Figure 7 provides a schematic representation of albiglutide treated subjects with elevated GGT levels.

- 24 albiglutide treated subjects had on-therapy elevated GGT.
  - 9/24 had normal baseline values and 15/24 had elevated baseline values
  - 3 subjects had elevated GGT values and ALT/AST values > 3x ULN.  
Narratives for these subjects are briefly described below.
- 14 comparator subjects had on-therapy elevated GGT
  - 3/14 had normal baseline values
  - 1 subject had increased GGT values and an associated ALT/ AST >3 x ULN

**Figure 7: P3-ISP AEs of Gamma Glutamyl Transferase in the Albiglutide Group**



CS: clinically significant values ( $\geq 3XULN$ ), CNS= clinically non-significant values ( $>$  baseline and  $< 3XULN$ )  
 Source: ISS Figure 40, Page 634.

Narratives for three albiglutide subjects with elevated GGT values and AST/ALT  $> 3x$  ULN are briefly described below:

**Subject 1464179011 (GGT and ALT elevation):** 49 year old female with normal baseline labs experienced elevations in ALT (peak 389 u/L ULN=48) and GGT (peak 1556 U/L ULN=45), 56 days after the sixth dose of albiglutide. Study drug was discontinued 6 week prior for injection site reaction. The subject started Tricor on December 7, 2012 at which time ALT (29 U/L), AST (18 U/L) and GGT (32 U/L) levels were normal. On January 25, 2011 serum ALT had increased to 195 U/L, AST was 78U/L and GGT 1524U/L. Ultrasound of the liver revealed mild fatty liver. MRI revealed cystic hepatic lesions. The subject did not report use of any alcohol, herbs, complimentary or alternative medicines. Viral serologies for hepatitis, CMV and EBV were normal. Tricor was discontinued on January 31, 2011 and follow up labs from March 29, 2011 demonstrated a decrease in liver enzymes [ALT 167 U/L, AST 63 U/L and GGT levels were not provided].

**Reviewer Comment:** *The etiology of hepatocellular injury is confounded by the introduction of Tricor. A relationship between the administration of Tricor and LFT abnormalities cannot be excluded in this case and is suggested by the temporal association between hepatic enzyme increase following Tricor*

***introduction and subsequent decline in hepatic enzyme levels after Tricor discontinuation.***

**Subject 3669754980 (ALT increased):** 57-year old Asian male with elevated baseline ALT of 59 U/L developed an increase in liver enzymes on study day 336; ALT (369 U/L, ULN =48) and AST (208 U/L, ULN = 42) GGT (128 U/L, ULN =65). The subject did not have a past medical history of liver disease. He consumed an average of 1 unit of alcohol per week. CT scan was remarkable for fatty infiltration of the liver. Study drug was discontinued (ALT 199 U/L, AST 129 U/L and GGT 96 U/L). One month post discontinuation, follow up labs remained elevated (ALT 200 U/L and AST 129 u/L, no GGT). The investigator concluded that there was a reasonable possibility that the increase of serum aminotransferase levels may have been caused by the investigational product.

***Reviewer Comment: This case was review by Dr. Avigan who agreed with the possibility of a drug induced injury and noted that “since diagnostic serological studies for viral hepatitis or other systemic conditions were not provided in this case, the presence of any of these processes as a background phenomenon cannot be excluded.***

The following narrative was provided after an information request was sent to the sponsor.

**Subject 3636755987 (Hepatic Cirrhosis):** 63 year old male with a history of back pain, possible basal cell carcinoma of the scalp, cholecystitis and cholecystectomy received the first dose of study drug on May 21, 2009 and glycemic rescue medication (not specified) on 31 Aug 2009. The last dose of investigational product was received on July 22, 2010 due to the site being closed by GSK following repeated noncompliance. During follow-up on study day 546 (120 days after the last dose of investigational product), the subject was found to have **hepatic cirrhosis**. He presented to the ED on November of 2010 with abdominal pain and a 2 month history of nausea, vomiting and a 20 pound weight loss. A CT scan of the abdomen revealed cirrhosis, splenomegaly, mild ascites and a thrombus to the main and right portal veins consistent with acute thrombosis superimposed on chronic thromboses. Hepatitis B and C serologies were negative. He did not consume alcohol and was a former tobacco user who last used in 1984. Additional information was not provided as the subject was lost to follow-up. Hepatic labs are detailed in the table below.

Date	ALT (Reference range 0-48 U/L) <sup>a</sup>	AST (Reference range 0 – 42 U/L) <sup>a</sup>	GGT (Reference range 0 – 65 U/L) <sup>a</sup>	Alkaline phosphatase (Reference range 20 125 U/L) <sup>a</sup>	Bilirubin (Reference range 0-22 µmol/L) <sup>a</sup>
14 May 2009 (week 1)	38	37	177	122	10
28 May 2009	46	49	236	126	10

22 Jun 2009	44	40	192	128	6
28 Jul 2009	46	115	262	115	10
18 Aug 2009	50	73	188	106	10
08 Oct 2009	41	39	194	108	8
28 Jan 2010	53	58	185	109	12
21 Apr 2010	72	127	204	102	12
19 May 2010	44	54	159	109	6
29 Jul 2010 (end of treatment)	69	151	247	162	10
23 Sep 2010	100	143	1690	1032	10
(b) (6)	99	385	850	722	14

<sup>a</sup> Values from the central laboratory.

**Reviewer Comment:** *Review of the laboratory data reveals that the subject experienced an elevation of AST/ALT and GGT levels from baseline prior to discontinuing study drug. Although a relationship to study drug cannot be excluded the subject was lost to follow-up and further diagnostic testing and evaluation for the etiology of cirrhosis was not done. The subject did not undergo a liver biopsy which would be the gold standard in diagnosing cirrhosis. In addition assessment for other possible inciting factors such as a history of hemochromatosis, Wilson’s disease, bile duct pathology, nonalcoholic fatty liver disease and presence of veno-occlusive disease which would be valuable with the presence of hepatic thrombus noted on CT was not conducted.*

*The clinical relevance of the higher incidence of increased GGT levels in the albiglutide group compared to both placebo and all comparators has not been fully elucidated. However this imbalance should be labeled and monitored in future studies and the applicant should conduct a gallbladder emptying study to better elucidate a potential relationship.*

## Serious Hepatobiliary Adverse Events

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

#### Albiglutide vs. Placebo

Overall serious events in the hepatobiliary SOC occurred in 0.1% (1/923) of albiglutide treated subjects vs. 0.4% (2/468) of placebo treated subjects.

#### Albiglutide vs. All Comparators

As described in Table 47, a total of 12 subjects reported on-therapy liver SAEs (4 albiglutide vs. 8 all comparators). Overall serious events in the hepatobiliary SOC occurred in 0.2% (4/2116) of albiglutide treated subjects vs. 0.3% (7/2284) of placebo

treated subjects. Most events in the albiglutide group were for single events of cholecystitis and cholelithiasis. One subject in the albiglutide group had an event coded as drug induced liver injury.

**Table 47: P3-ISP: On-therapy Serious Liver Adverse Events by SOC, High Level Term, and Preferred Term - Albiglutide vs. All Comparators**

	All Comparators (N=2284)	Albiglutide (N=2116)
System Organ Class		
High Level Term	n (%)	n (%)
Preferred Term		
<b>Investigations</b>		
<b>Liver function analyses</b>	1 (0.0)	0
Liver function test abnormal	1 (0.0)	0
<b>Hepatobiliary disorders</b>		
Any event	7 (0.3)	4 (0.2)
<b>Cholecystitis and Cholelithiasis</b>	7 (0.3)	3 (0.1)
Cholecystitis	0	1 (0.0)
Cholecystitis chronic	0	1 (0.0)
Cholelithiasis	2 (0.1)	1 (0.0)
Cholecystitis acute	5 (0.2)	0
<b>Hepatocellular damage and hepatitis NEC</b>	0	1 (0.0)
Drug-induced liver injury	0	1 (0.0)

Source Data: ISS Table 194 page 591. AE = adverse event; NEC = not elsewhere classified; SOC = System Organ Class. Note: On-therapy events are 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. On-therapy AEs that are flagged by the investigator as a liver event are presented in this summary. For each level of summarization, a subject was counted once if the subject reported 1 or more events. Percentages are based on the number of subjects in each treatment grouping.

1. Num. of AEs = the total number of AEs at each level of summarization. Density per 100 person-years = 100 \* (number of AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the treatment period being summarized.

Narratives for SAEs in the albiglutide group are described briefly:

Subject 1249486003 (**chronic cholecystitis**): 46-year old male with a past history of myasthenia gravis (treated with mycophenolate) and dyslipidemia (treated with simvastatin) developed nausea, vomiting and right upper quadrant pain requiring hospitalized on study 123. Study medication was held. Liver enzymes and lipase were not elevated at admission and the subject had a laparoscopic cholecystectomy performed to remove the gall bladder. Pathology revealed a benign gallbladder with chronic inflammation without gallstones. Two weeks the subject's albiglutide was restarted at 30 mg week. On study day 173 the subject experienced moderate vomiting

and the study medication was discontinued. The investigator considered there was a reasonable possibility that the events of **chronic cholecystitis** and vomiting may have been caused by the albiglutide and/or insulin glargine.

Subject 3422754987 (**cholelithiasis**): 57-year old male with a history of dyslipidemia (treated with simvastatin), leg cramps (treated with gabapentin 300 mg every other day) and biliary disease (etiology not specified in the narrative), also consumed an average of 1 unit of alcohol per week. On study day 154 the subject experienced severe cholelithiasis and was hospitalized. Per the narrative liver enzymes, amylase and lipase were elevated and a computed tomography scan showed gallstones and gallbladder wall thickening, cholecystitis, and gallbladder wall calcification and intrahepatic and extrahepatic biliary ductal dilation. He underwent open cholecystectomy and pathology revealed chronic cholecystitis and **cholelithiasis**. The investigator considered there was no reasonable possibility that the event of cholelithiasis may have been caused by the investigational product.

**Results from Laboratory Tests Performed**

Date	HbA1c (reference range: < 6.5 % TL HB) <sup>a</sup>	Amylase (reference units: U/L) <sup>b</sup>	Lipase (reference units: U/L) <sup>b</sup>	AST (reference range: 0 – 42 U/L) <sup>a</sup>	ALT (reference range : 0 – 48 U/L) <sup>a</sup>	Total bilirubin (0 – 22 UMOL/L) <sup>a</sup>
19 Jun 2009 (Baseline)	6.8 <sup>a</sup>			19 <sup>a</sup>	17 <sup>a</sup>	16 <sup>a</sup>
06 Nov 2009 (Week 20)	6.5 <sup>a</sup>			26 <sup>a</sup>	29 <sup>a</sup>	18 <sup>a</sup>
20 Nov 2009		71 <sup>b</sup>	20 <sup>b</sup>			
04 Dec 2009 (Week 24)				34 <sup>a</sup>	28 <sup>a</sup>	20 <sup>a</sup>
30 Dec 2009 (Week 28)	6.3 <sup>a</sup>					14 <sup>a</sup>
26 Feb 2010 (Week 36))	6.4 <sup>a</sup>			20 <sup>a</sup>	14 <sup>a</sup>	14 <sup>a</sup>

a. Values are from the central laboratory.

b. Values are from the local laboratory. Reference ranges were not provided.

**Reviewer Comment: The likely etiology is cholelithiasis.**

Subject 7764753989 (**Cholecystitis**) is described below under the 4MSU as the event was not resolved at the time of BLA submission.

Subject 1028179043-(**Drug Induced Liver Injury**): 61-year old female with a history of osteoarthritis, dyslipidemia and heart burn on naproxen experienced elevated liver lab findings (ALT 499 U/L, AST 511 U/L, T. bili 1.3 mg/dl, GGT 581 U/L) the same day as the second dose of albiglutide (Day 8), for which she was hospitalized and the study medication was discontinued. Liver function tests were normal at screening and baseline. Two days prior to starting study medication she saw a physician in Mexico while traveling and was given scopolamine for a complaint of “burning stomach pain”. The subject was asymptomatic and without scleral icterus or darkening of urine. She

denied any new over-the-counter medications or exposures and denied use of alcohol, herbals, complimentary or alternative medicines and use of acetaminophen. Imaging indicated liver hypertrophy with fatty liver echotexture and mild fatty liver infiltrate without focal lesions. There were gallstones present and there were no other biliary ductal lesions or portal/hepatic vein abnormalities reported. The event was coded by the sponsor as severe **drug-induced hepatitis**. The investigator concluded there was a reasonable possibility that this event of ‘drug-induced hepatitis’ may have been caused by albiglutide. Serologic testing included Hep B core Ab/ Hep B S Ag negative, Hep A IgM negative, HCV PCR undetectable (< 43 IU/ ml), Hep E IgM negative, ANA negative, Epstein-Barr VCA IgM negative, Actin/ LKM Ab IgG negative, CPK 76 U/L (ULN 190), LDH 146 U/L (ULN=250), Lipase 26 U/L (ULN=60), and Amylase 42 U/L (ULN=103). Lab data is detailed in the table below. Imaging indicated liver hypertrophy with fatty liver echotexture and mild fatty liver infiltrate without focal lesions. There were gallstones present. The event was coded by the sponsor as severe **drug-induced hepatitis**. The investigator concluded there was a reasonable possibility that this event of ‘drug-induced hepatitis’ may have been caused by albiglutide.

**Laboratory Tests Results**

Date	ALT (ULN=48)	AST (ULN=42)	GGT (ULN=45)	Alkaline Phosphatase (ULN=125)	Total Bilirubin (ULN=1.3)	Direct Bilirubin (ULN=0.4)
21 Sep 2010	25 U/L	20 U/L	68 U/L	109 U/L	1.0 mg/dl	0.2 mg/dl
21 Oct 2010	29	24	68	102	1.1	0.1
3 Nov 2010	27	22	75	110	1.1	0.2
(b) (6)	499	511	581	226	5.6	2.5
15 Nov 2010	180	40	412	169	1.3	0.3
18 Nov 2010	94	27	--	151	0.9	--
22 Nov 2010	46	23	--	133	1.1	--
1 Dec 2010	24	15	152	115	1.0	0.2

**Reviewer Comment: The etiology of hepatocellular injury is confounded in this case by the presence of gallstones and recent international travel to Mexico. The temporal association of enzyme elevation to the first dose of albiglutide is may suggest a potential relationship to study drug. This case was reviewed by Dr. Avigan who agreed with the investigator’s assessment noting “The reported event is consistent with an episode of acute hepatocellular injury characterized both by a rapid onset and rapid resolution. With the accompanying mild cholestatic changes in this case, the serial biochemical measures of liver injury are consistent with but not entirely typical of “Hy’s Law”.”**

**Hepatobiliary Adverse Events Leading to Withdrawal (AEWD)**

PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

As described in Table 48 a slightly greater proportion of albiglutide treated subjects withdrew from active treatment for liver related adverse events (7.5% vs. 5.7%, respectively). Narratives for AE withdrawals in the albiglutide treatment group are described below.

**Table 48: P3-ISP On-therapy Liver Adverse Events Leading to Withdrawal of Active Treatment – Albiglutide vs. All Comparators**

	All Comparators	Albiglutide
	(N=2284)	(N=2116)
<b>System Organ Class Preferred Term</b>	<b>n (%)</b>	<b>n (%)</b>
Any AE leading to withdrawal of active treatment	130 (5.7)	159 (7.5)
<b>Investigations</b>		
Any event	13 (0.6)	14 (0.7)
ALT increased	0	4 (0.2)
Liver function test abnormal	1 (0.0)	2 (0.1)
Hepatic enzyme increased	1 (0.0)	0
<b>Hepatobiliary disorders</b>		
Any event	1 (0)	2 (0.1)
Cholelithiasis	0	1 (0.0)
Drug-induced liver injury	0	1 (0.0)
Hepatic steatosis	1 (0.0)	0

Source Data: ISS Table 196, Page 593

Subject 3865753981: 62-year old male with a history of non-alcoholic fatty liver disease, one unit of alcohol consumption per week and history of mild baseline elevated liver enzymes, developed elevated liver function tests on study day 28. Additional medical conditions included hypertension (treated with lisinopril), dyslipidemia (treated with simvastatin), erectile dysfunction (treated with tadalafil) and gastroesophageal reflux (treated with esomeprazole). Ultrasound indicated an enlarged liver consistent with fatty changes and focal cystic hepatic lesions. The subject did not have a gallbladder and the common bile duct was not well visualized. The narratives states the subject did use herbals and complementary medicine. Follow up information from the investigator noted that the subject used multivitamins. Study medication was withdrawn. The investigator considered there was a reasonable possibility that the event of raised liver function tests may have been caused by the investigational product. Follow up information obtained from the sponsor revealed that transabdominal ultrasound imaging

was performed and indicated a hypertrophic liver with fatty infiltration (=25%) and focal cystic hepatic lesions, but was negative for ascites and portal/hepatic vein abnormalities. The subject did not have a gallbladder and the common bile duct was not well visualized. Liver biopsy was not performed. The subject tested negative to Hepatitis B, Hepatitis C and HIV at screening and was again non-reactive to Hepatitis B surface antigen when retested at the time of liver enzyme elevation. Follow up laboratory data is detailed below with any new information (not previously provided with the original BLA shaded gray).

**Table 49: Liver Function Tests for Subject 3865753981**

Date	ALT (alanine aminotransferase) (Reference Range: 0-48 U/L) a	AST (aspartate aminotransferase) (Reference Range: 0-42 U/L) a	GGT (gamma glutamyl transferase) (Reference Range: 0-65U/L)	Alkaline Phosphatase (reference Range: 20 – 125 U/L)
20 Oct 2009 (Week -6)	99	76	53	44
23 Nov 2009 (Week -2)	105	77	70	72
07 Dec 2009 Baseline	134	96	89	73
14 Dec 2009 Week 1	119	76	82	79
21 Dec 2009 Week 2	128	83	82	73
04 Jan 2010 Week 4	186	141	83	72
Albiglutide stopped 04 Jan 2010				
07 Jan 2010 Liver events assessment; event	182	109	-	76
18 Jan 2010 Liver chemistry follow up; event	141	98	-	68
01 Feb 2010 Liver chemistry follow up; event	149	127	-	73
22 Feb 2010 Liver chemistry follow up; event stop date	68	48	-	68
01 Apr 2010	52	34	38	70
27 May 2010	53	41	38	72
10 Jan 2011 (1 year annual follow-up)	165	122	81	146

Values are from the central laboratory.

**Reviewer Comment: The etiology of hepatocellular injury is confounded by baseline elevations in liver enzymes, underlying fatty liver disease, and an unclear significance of hepatic cystic lesions. The persistence of enzyme elevations 1 year post study drug withdrawal suggest that an alternate etiology cannot be excluded.**

Subject 3628755987: 34-year old male without a past medical history or social history of alcohol consumption, developed an elevation in liver enzymes at study week 48 (AST 73 U/L). Study medication was continued and ALT and AST levels increased. Additional imaging was not performed. Study drug was withdrawn around week 78. The investigator considered there was a reasonable possibility that the event of elevated liver function test may have been caused by the investigational product.

Date	ALT (range: ULN 48 U/L)	AST (range: ULN 42 U/L)	Total Bilirubin (reference range: ULN 1.2 mg/dL)
15 Oct 2009 (Baseline)	17	12	0.9
10 Dec 2009 (Week 8)	20	18	1.6
24 Jun 2010 (Week 36)	45	24	0.7
16 Sep 2010 (Week 48)	73	35	1.0
19 Oct 2010 (Week 52)	96	46	1.2
13 Jan 2011 (Week 65)	139	50	1.0
15 Apr 2011 (Week 78)	192	93	0.9
03 May 2011 (Week 78)	200	90	1.2
16 May 2011 (End of Treatment)	176	77	1.3

**Reviewer Comment: The narrative provided lacks sufficient details to determine a causal relationship to study drug.**

Subject 3578754988 : 53-year-old male developed acute sclera icterus, jaundice, nausea, abdominal discomfort, bloating and darkened urine at study week 78. Serum ALT and bilirubin values were 2986 U/L (62.2xULN) and 192 micromol/L (11.2 mg/dL; 8.7xULN), respectively. Hepatitis B surface antigen was positive. A diagnosis of acute hepatitis B was made and the subject was withdrawn from the study.

**Reviewer Comment: Dr. Avigan agreed with the diagnosis of Hepatitis.**

Subject 3669754980: 57-year old Asian male with elevated baseline ALT of 59 U/L developed an increase in liver enzymes on study day 336; ALT (369 U/L, ULN =48) and AST (208 U/L, ULN = 42) GGT 128 U/L, ULN =65). CT scan was remarkable

for fatty infiltration of the liver. Study drug was discontinued and there was a decline in LFTs 4 months later (ALT 93 U/L, AST 51U/L, GGT 54 U/L). The investigator concluded that there was a reasonable possibility that the increase of serum aminotransferase levels may have been caused by the investigational product.

*Dr. Avigan reviewed this case and agreed with possibility of a drug induced injury with the limited information available. "Since diagnostic serological studies for viral hepatitis or other systemic conditions were not provided in this case, the presence of any of these processes as a background phenomenon cannot be excluded."*

Subject 3599757986 71-year old male, 455 days after the first dose of investigational product the subject experienced moderate elevated alanine aminotransferase ALT (492 U/L), AST (168 U/L) and GGT (505 U/L) prompting immediate discontinuation of the study drug. The investigator concluded that there was a reasonable possibility that the elevations of aminotransferases may have been caused by the investigational product.

*Dr. Avigan reviewed this case as a possibility of a drug induced injury (with the limited information available).*

Subject 3663753989: 53 year old female experienced an acute transient rise in liver test results on study day 15: ALT: 441 U/L, AST: 222 U/L, GGT: 482 U/L, ALP: 212 U/L, T. bili: 0.5 mg/dl. Study drug was discontinued. The investigator considered there was no reasonable possibility that the event was caused by the investigational product

*Dr. Avigan reviewed the case and concluded that with the limited information these cases are consistent with mild liver injury and suggest a causal association with exposure to the study drug.*

*Dr. Avigan states that "there is a plausible causal association of idiosyncratic episodes of mild hepatocellular injury with exposure to the GLP-1 mimetic agent which all rapidly resolved upon drug discontinuation. With rises of GGT and slight rises of ALP in some of the cases there is the hypothetical possibility that the injuries were associated with transient cholestasis, either intra-hepatic in nature or possibly linked to reduced extrahepatic biliary flow and gallbladder motility that may be caused by some GLP-1 mimetic agents. The sponsor should be encouraged to actively follow-up and evaluate the clinical characteristics and diagnostic test results of all cases of albiglutide-associated liver injury that are reported in the future."*

## **Liver Function Threshold Analyses**

### **PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)**

Abnormal liver function tests results are detailed in Table 50 below. A higher percentage of subjects in the albiglutide group (0.2 % /2116 subjects) compared to all comparators (1 /2284 subjects) experienced Alt  $\geq$  8x ULN.

**Table 50: P3-ISP: Liver Function Tests (SI Units) of Clinical Concern by Analysis Visit – Albiglutide versus All Comparators**

	All Comparators N=2284 (%)	Albiglutide N=2116 (%)
<b>Alanine aminotransferase</b>		
Any On-therapy Visit		
n	2277	2103
$\geq 2 \times$ ULN	76 (3.3)	65 (3.1)
$\geq 3 \times$ ULN	20 (0.9)	18 (0.9)
$\geq 5 \times$ ULN	6 (0.3)	6 (0.3)
$\geq 8 \times$ ULN	1 (0.0)	4 (0.2)
$\geq 10 \times$ ULN	1 (0.0)	3 (0.1)
$\geq 3 \times$ ULN and Bilirubin $\geq 2 \times$ ULN	3 (0.1)	2 (0.1)
<b>Aspartate aminotransferase</b>		
Any on-therapy visit		
n	2277	2103
$\geq 2 \times$ ULN	63 (2.8)	43 (2.0)
$\geq 3 \times$ ULN	16 (0.7)	16 (0.8)
$\geq 5 \times$ ULN	4 (0.2)	3 (0.1)
$\geq 8 \times$ ULN	2 (0.1)	2 (0.1)
$\geq 10 \times$ ULN	1 (0.0)	2 (0.1)
$\geq 3 \times$ ULN and Bilirubin $\geq 2 \times$ ULN	0	0
<b>Bilirubin</b>		
Any on-therapy visit		
n	2277	2103
$\geq 1.5 \times$ ULN	17 (0.7)	12 (0.6)
$\geq 2 \times$ ULN	6 (0.3)	3 (0.1)
$\geq 3 \times$ ULN	3 (0.1)	2 (0.1)
$\geq 5 \times$ ULN	2 (0.1)	1 (0.0)
$\geq 8 \times$ ULN	1 (0.0)	1 (0.0)
$\geq 10 \times$ ULN	1 (0.0)	1 (0.0)
<b>Gamma-glutamyl transferase (U/L)</b>		
Any On-therapy visit		
n	2277	2103
> 3 x ULN	87 (3.8)	93 (4.4)

SCS Table 65 pg 205 Note: Baseline is defined as the last available assessment on or prior to the first dose of study medication. ULN = upper limit of normal reference range. Subjects may have been counted in more than 1 category. Source Data: Phase III Integrated Safety Database (Studies GLP108486, GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, and GLP114179)

Subject Meeting the Biochemical Criteria for Hy's Law.

Two subjects in the albiglutide group and 3 subjects in the all comparators group had ALT  $\geq 3 \times$  ULN and a bilirubin  $\geq 2 \times$  ULN.

In the albiglutide group narratives for Subject 1028179043 (under SAE) and Subject 3578754988 (under AEWD) are described above and were also reviewed by the liver team.

#### Subject With ALT rise $\geq 5 \times$ the ULN

A total of 12 subjects had on-therapy ALT values  $\geq 5 \times$  ULN (6 subjects in the all comparators group and 6 subjects in the albiglutide group).

Albiglutide Group Subjects: 3663753989, 3669754980, 3599757986, 1028179043, 3578754988 are described above and were reviewed by the OSE liver team.

Subject 1200179009: 52-year old female developed an increase in ALT 356 (T. bili within normal limits) on approximately study day 40. Study medication was discontinued and restarted without liver function test abnormalities. The investigator thought that there was no reasonable possibility that the event of elevated ALT may have been caused by the albiglutide

***Reviewer Comment: The negative rechallenge demonstrated by the reintroduction of study drug without liver enzyme abnormalities confounds an assessment of study drug causality. Dr. Avigan reviewed the case and determined that the “The transient episode of acute liver injury at the time of administration of the 6<sup>th</sup> weekly dose of albiglutide is consistent with a hepatocellular pattern of injury”.***

#### 4MSU LIVER EVENTS

During the incremental period, 8 additional subjects (0.6%) in the albiglutide treatment group and 16 additional subjects (1.0%) in the all comparators treatment group reported on-therapy liver-related AEs. In the albiglutide treatment group, the most frequently reported preferred term events were cholecystitis and cholelithiasis (0.2%, 3/1427 subjects, respectively). Among subjects in the all comparators group, the most frequently reported events were for hepatic steatosis and aspartate aminotransferase increased.

#### Serious Adverse Events

In the all comparators group the overall incidence of SAE in the hepatobiliary disorders SOC was 0.3%, 4/1595 for all comparators and 0.1%, 2/1427 in the albiglutide arm. Of

the two 2 albiglutide subjects (0.1%) with a SAEs one event lead to study drug discontinuation). These serious events are briefly described below.

Subject 5779755989: 56 year old female with a history of chronic cholelithiasis developed sclerosing atrophic cholecystitis 3 years after starting study drug [ALT 343 U/L (> 5 X ULN)].

Subject 7764753989: 68-year old male with a history if dyslipidemia was found to have a gallstone on study day 853. The event of cholecystitis was considered not resolved at the time of BLA submission. Follow up with the 4MSU revealed that the subject had a cholecystectomy for gallstones and study drug was discontinued.

#### Laboratory analysis:

There were no cases of biochemical Hy's law in the safety update (ALT  $\geq 3 \times$  ULN and Bilirubin  $\geq 2 \times$  ULN: 0 subjects in any treatment group)

### CUMULATIVE LIVER EVENTS

Overall liver related adverse events were similar between albiglutide and all comparators. (3.9% and 4%, respectively). The greatest imbalance was observed for events of GGT increased and was not in favor of albiglutide (1.2%, 26/2116 vs. 0.7%, 15/ 2284).

**Table 51: Cumulative On-Therapy Liver-Related Adverse Events (Phase III Integrated Safety Population)**

System Organ Class High Level Term Preferred Term	All Comparators (N=2284)		Albiglutide (N=2116)	
	n (%)	Number of AEs/Density <sup>1</sup>	n (%)	Number of AEs/Density <sup>1</sup>
Any event	91 (4.0)	120/2.78	82 (3.9)	111/2.79
<b>Investigations</b>				
Any event	52 (2.3)	68/1.57	50 (2.4)	69/1.73
Liver function analyses	51 (2.2)	67/1.55	50 (2.4)	69/1.73
Gamma-glutamyltransferase increased	15 (0.7)	16/0.37	26 (1.2)	28/0.70
Alanine aminotransferase increased	16 (0.7)	16/0.37	15 (0.7)	15/0.38
Hepatic enzyme increased	12 (0.5)	12/0.28	10 (0.5)	10/0.25
Aspartate aminotransferase increased	11 (0.5)	11/0.25	9 (0.4)	20/0.25
Liver function test abnormal	7 (0.3)	8/0.19	4 (0.2)	5/0.13
Transaminases increased	1 (0.0)	2/0.05	1 (0.0)	1/0.03
Blood bilirubin increased	1 (0.0)	1/0.02	0	0
Gamma-glutamyltransferase	1 (0.0)	1/0.02	0	0
Hepatobiliary imaging procedures	1 (0.0)	1/0.02	0	0
Hepatobiliary scan abnormal	1 (0.0)	1/0.02	0	0
<b>Hepatobiliary disorders</b>				
Any event	45 (2.0)	52/1.20	33 (1.6)	42/1.05
Cholecystitis and cholelithiasis	21 (0.9)	23/0.53	17 (0.8)	20/0.50

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Cholelithiasis	13 (0.6)	14/0.32	10 (0.5)	10/0.25
Cholecystitis.	2 (0.1)	2/0.05	7 (0.3)	8/0.20
Cholecystitis acute	7 (0.3)	7/0.16	1 (0.0)	1/0.03
Cholecystitis chronic	0	0	1 (0.0)	1/0.03
Hepatocellular damage and hepatitis NEC	17 (0.7)	18/0.42	13 (0.6)	15/0.38
Hepatic steatosis	14 (0.6)	15/0.35	13 (0.6)	14/0.35
Drug-induced liver injury	0	0	1 (0.0)	1/0.03
Hepatitis	1 (0.0)	1/0.02	0	0
Nonalcoholic steatohepatitis	2 (0.1)	2/0.05	0	0
Hepatobiliary signs and symptoms	3 (0.1)	3/0.07	4 (0.2)	4/0.10
Hepatomegaly	2 (0.1)	2/0.05	4 (0.2)	4/0.10
Hepatosplenomegaly	1 (0.0)	1/0.02	0	0
Gallbladder disorders NEC	0	0	2 (0.1)	2/0.05
Biliary dyskinesia	0	0	1 (0.0)	1/0.03
Gallbladder pain	0	0	1 (0.0)	1/0.03
Hepatic and hepatobiliary disorders NEC	1 (0.0)	1/0.02	1 (0.0)	1/0.03
Hepatic lesion	1 (0.0)	1/0.02	1 (0.0)	1/0.03
Hepatic enzymes and function abnormalities	4 (0.2)	4/0.09	0	0
Hepatic function abnormal	1 (0.0)	1/0.02	0	0
Hypertransaminasaemia	3 (0.1)	3/0.07	0	0
Hepatic fibrosis and cirrhosis	1 (0.0)	1/0.02	0	0
Hepatic cirrhosis	1 (0.0)	1/0.02	0	0
Hepatic vascular disorders	1 (0.0)	1/0.02	0	0
Hepatic artery stenosis	1 (0.0)	1/0.02	0	0
Obstructive bile duct disorders (excluding neoplasms)	1 (0.0)	1/0.02	0	0
Bile duct stone	1 (0.0)	1/0.02	0	0

Source Data: 120-day Table SUC7-20. (The 5 ongoing Phase III studies include the following: GLP112753, GLP112754, GLP112755, GLP112756, and GLP112757.)

CI = confidence interval, NA = not applicable, NEC = not elsewhere classified

Note: On-therapy events are those that have a start date on or after the first day of study medication and within 56 days after the end of study medication. This summary presents on-therapy adverse events (AEs) coded to the hepatobiliary disorders or investigations system organ class. For each level of summarization, a subject is counted once if the subject reported one or more events.

Percentages are based on the number of subjects in each treatment group. The system organ class (SOC) and preferred terms within the SOC are presented by decreasing frequency of incidence for all treatment groups combined.

1. Number of AEs = the total number of AEs at each level of summarization. Density per 100 person-years =  $100 \times (\text{number of AEs} / \text{person-years})$ , where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the treatment period being summarized.

2. The relative risk and 95% CI for the albiglutide treatment grouping compared with the comparison treatment grouping are calculated using the Cochran-Mantel-Haenszel estimate of relative risk stratified by study.

### Serious Adverse Events

Overall in the hepatobiliary disorders SOC 0.2%, 5/2166 of albiglutide treated subjects and 0.4%, 10/2284 of all comparators had a serious event. In the albiglutide arm most events were related to cholecystitis and 1 subject had drug induced liver injury.

## RENAL STUDY (GLP114130) LIVER EVENTS

Adverse liver events were comparable between the treatment groups and there were no serious events in the albiglutide group. There were no subjects in the albiglutide arm that had an ALT elevation  $\geq 5 \times \text{ULN}$  or  $\geq 3 \times \text{ULN}$  with an elevated bilirubin. There was one subject in the renal study randomized to sitagliptin with an ALT elevation  $> 5 \times \text{ULN}$ .

**Table 52: Renal Study (GLP114130) On-Therapy Liver Adverse Events in at least 1 albiglutide treated subject:**

System Organ Class (SOC)  Preferred Term (PT)	Sitagliptin (N=246)	Albiglutide (N=249)
	N (%)	N (%)
<b>Investigations</b>		
Alanine aminotransferase increased	1 (0.4)	1 (0.4)
Gamma-glutamyltransferase increased	0	1 (0.4)
<b>Hepatobiliary disorders</b>		
Any event	6 (2.4)	2 (0.8)
Cholecystitis	1 (0.4)	1 (0.4)
Cholelithiasis	1 (0.4)	1 (0.4)

Source Data: CSR 114130 Table 73, Page 225. AE = adverse event.

## HYPOGLYCEMIA

Hypoglycemic events were classified based on ADA severity criteria. Overall in the P3-ISP pre-rescue hypoglycemic events were higher in subjects treated with albiglutide compared to placebo (11.9% vs. 7.3% of subjects, respectively). A higher incidence of severe and documented symptomatic hypoglycemia occurred in albiglutide treated subjects compared to the placebo group. There were no SAEs in the albiglutide arm. A lower proportion of subjects in the albiglutide group experienced pre-rescue hypoglycemia compared to all comparators (18.5% vs. 22.6 %, respectively). Albiglutide treated subjects on background insulin or sulfonylureas experienced a greater incidence of hypoglycemic events compared to subjects not on hypoglycemia inducing agents. Individual study review revealed that in the monotherapy study the incidence of severe and documented symptomatic hypoglycemia was similar between albiglutide 30 mg and placebo. Individual study analysis also confirmed the higher incidence of severe and documented symptomatic hypoglycemia in subjects taking albiglutide with insulin or sulfonylureas.

On-therapy hypoglycemic events were flagged by the investigator on eCRFs and classified for severity based on the American Diabetes Association (ADA)-defined severity categories below.

- **Severe hypoglycemia:** an event requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.
- **Documented symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration  $\leq 70$  mg/dL.
- **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration  $\leq 70$  mg/dL.
- **Probable symptomatic hypoglycemia:** an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration  $\leq 70$  mg/dL).
- **Relative hypoglycemia:** an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration  $> 70$  mg/dL.

The applicant notes that in approximately 2% of total hypoglycemic events, the investigator-reported classification of severity did not match the recorded glucose levels. As a result in the P3-ISP, these investigator-reported events were reclassified for “derived severity” based on ADA definitions and the associated recorded glucose levels.

The criteria for derived severity were as follows:

- If the investigator assigned severity was probable symptomatic or relative and the corresponding blood glucose level was  $\leq 70$  mg/dL the event was reclassified to a derived ADA severity of documented symptomatic.
- If the investigator assigned severity was documented symptomatic or probable symptomatic and the corresponding blood glucose level was  $> 70$  mg/dL, the event was reclassified to have a derived ADA severity of relative.
- If the investigator assigned severity was documented symptomatic or relative and the corresponding blood glucose level was missing the event was reclassified to have a derived ADA severity of probable symptomatic.
- If the investigator assigned severity is asymptomatic and the corresponding blood glucose level is  $> 70$  mg/dL or is missing then the event was not considered a hypoglycemic event from a derived ADA severity perspective

***Reviewer Comment: My review of hypoglycemic events in the albiglutide program focuses on pre-rescue hypoglycemia to avoid confounding by rescue medications. In addition derived severity events were primarily considered since they represent severity classification based on ADA definitions with recorded glucose values.***

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

Table 53 summarizes pre-rescue hypoglycemic events in the P3-ISP by treatment comparison arms.

#### Albiglutide vs. Placebo

A higher incidence of hypoglycemic events occurred in the albiglutide group vs. placebo (11.9% vs. 7.3% of subjects, respectively). There were no SAEs of hypoglycemia in either treatment group. Two albiglutide treated subjects withdrew from treatment vs. none in the placebo arm. There were 5 severe hypoglycemic events in 4 subjects in the albiglutide arm vs. 0 in placebo. Similarly a higher proportion of subjects receiving albiglutide (6.2%) experienced a documented symptomatic episode vs. placebo (3.8%).

#### Albiglutide vs. All Comparators

A lower proportion of subjects in the albiglutide group experienced pre-rescue hypoglycemia in the albiglutide group compared to all comparators (18.5% vs. 22.6 %, respectively). There were no hypoglycemic SAEs in the albiglutide arm and 4 subjects experienced 4 serious SAEs in the all comparators group. A small proportion of subjects were withdrawn from the study (0.1% in both groups). In the albiglutide group 7 subjects (0.3%) experienced 8 severe hypoglycemic events compared to 8 subjects (0.4%) experiencing 9 severe events of hypoglycemia in comparators. There was a higher incidence of documented symptomatic hypoglycemic events in the comparator arm vs. albiglutide (16.3 % vs. 11.7%, respectively).

### **Hypoglycemia withdrawal**

#### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

Brief descriptions of subjects who withdrew from albiglutide (n=2, 0.1%) treatment for hypoglycemia are detailed below.

Subject 3615757989: 71 year old female received study drug and metformin, and developed hypoglycemia (blood glucose value not provided) on study day 137(6 days after study medication was discontinued). Study drug was withdrawn due to the event.

Subject 3494753987: 66 year old female received study drug and metformin, and developed hypoglycemia on study day 1 for which study drug was withdrawn. Blood glucose values were not provided in the narrative.

**Table 53: Overview of On-therapy Hypoglycemic Events Prior to Hypoglycemia rescue by Treatment Group Comparisons (P3-ISP)**

	Albiglutide vs. All Comparators				Albiglutide vs. Placebo			
	All Comparators (N=2284)		Albiglutide (N=2116)		Placebo (N=468)		Albiglutide (N=923)	
	N (%)	# of events	n (%)	# of events	n (%)	# of events	n (%)	# of events
	Any on-therapy hypoglycemic event	516 (22.6)	2211	391 (18.5)	1342	34 (7.3)	84	110 (11.9)
On-therapy hypoglycemic event density <sup>1</sup>		80.24		50.54		17.33		25.36
<b>Severity</b>								
Severe	8 (0.4)	9	7 (0.3)	8	0	0	4 (0.4)	5
Documented symptomatic	373(16.3)	1607	248 (11.7)	912	18 (3.8)	47	57 (6.2)	198
Asymptomatic	106 (4.6)	205	100 (4.7)	152	1 (0.2)	2	20 (2.2)	26
<b>SAEs<sup>2</sup></b>								
Yes	4 (0.2)	4	0	0	0	0	0	0
No	512 (22.4)	2207	391 (18.5)	1342	34 (7.3)	84	110 (11.9)	364
<b>Withdrawn due to hypoglycemic event<sup>2</sup></b>								
Yes	3 (0.1)	3	2 (0.1)	2	0	0	2 (0.2)	2
No	513 (22.5)	2208	389 (18.4)	1340	34 (7.3)	84	108 (11.7)	362

Modified from ISS Table 109 page 330. # = number. On-therapy adverse events prior to hyperglycemia rescue that were flagged by the investigator as hypoglycemic events are presented in this summary. Subjects with more than 1 hypoglycemic event were counted in all categories reported except as noted in footnote 2 below.

1. The hypoglycemic adverse event (AE) incidence density per person-year = (number of hypoglycemic AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the treatment period being summarized.
2. Subjects with more than 1 hypoglycemic event are counted only once in the worst category.

## Severe Hypoglycemic Events

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

The overall proportion of subjects experiencing non serious severe hypoglycemic events prior to hyperglycemia rescue was similar in the albiglutide and all comparators groups (0.3 vs. 0.4%, respectively), with most events occurring within the first 26 weeks of treatment. In the albiglutide group 7 subjects experienced 8 severe hypoglycemic events prior to hyperglycemia rescue.

Review of the narratives for these severe events revealed that the majority (5/7 subjects in the albiglutide group) were simultaneously on a sulfonylurea. One of these events resulted in subject withdrawal from the study and is described below.

Subject 3639754987: 80-year old male on study drug, metformin and glyburide experienced a severe hypoglycemic episode on study day 9 (BG 48 (reference units not provided) and was withdrawn from the study.

Narratives for 2 albiglutide treated subjects experiencing severe hypoglycemic events not on background sulfonylurea or insulin are described below.

Subject 3556755987: 52-year-old man randomized to albiglutide on background metformin and pioglitazone experienced a severe hypoglycemic episode on study day 218 resulting in unconsciousness. Per the narrative the blood glucose was 68 mg/dL at the time of the event.]) The subject ate a small meal and saw a healthcare professional but was not hospitalized. No action was taken with the study medication due to the event.

**Reviewer Comment: The event was classified as severe due to the subject's loss of consciousness. While the recorded blood glucose at the time of the event was 68 mg/dL, it is unclear if this sample was drawn prior to any efforts to treat hypoglycemia.**

Subject 3530755988: 58-year-old woman randomized to albiglutide and on background metformin and pioglitazone experienced 3 hypoglycemic events on study day 1, 47 and 123, respectively. This subject did not meet hyperglycemic rescue criteria at any point during the study. The event on day 47 was categorized as severe due to the subject requiring immediate assistance at the location of the event (glucose drinks or supplements). Additional data was not provided.

**Reviewer Comment: Overall review of hypoglycemic narratives suggests that severe hypoglycemic events were more likely to occur in albiglutide treated subjects taking concomitant sulfonylureas.**

## Hypoglycemia on Background Sulfonylurea (SU) OR INSULIN

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

Due to the potential for insulin and insulin secretagogues (such as sulfonylureas) to cause hypoglycemia the applicant evaluated pre-rescue hypoglycemia events based on background insulin or sulfonylurea therapy.

#### Albiglutide vs. Placebo

The proportion of subjects with on-therapy hypoglycemic events prior to hyperglycemia rescue in subjects taking background insulin and/or SU was 22.9% (62 of 271 subjects) in the albiglutide group and 11.3% (13 of 115 subjects) in the placebo group compared with 7.4% (48 of 652 subjects) and 5.9% (21 of 353 subjects) not taking background insulin and/or SU in albiglutide and placebo subjects, respectively. Placebo subjects were generally rescued sooner.

#### Albiglutide vs. All comparators

Table 54 delineates pre-rescue hypoglycemia events based on background insulin or sulfonylurea (SU) therapy. The proportion of subjects experiencing on-therapy hypoglycemic events prior to hyperglycemia rescue was lower in the albiglutide group regardless of background insulin and/or SU when compared to all comparators. Approximately 27% of subjects treated with albiglutide and taking insulin or SU had an on-therapy hypoglycemic event compared to 34.2% in the all comparators group. Similarly albiglutide treated subjects not on background insulin or SU experienced less hypoglycemic events (6.6%) vs. all comparators not on insulin or SU (11.7%).

***Reviewer Comment: Overall hypoglycemic events were higher for both the albiglutide and all comparators treatment groups with background insulin and/or SU use as compared with subjects not taking background insulin and/or SU.***

### Hypoglycemic Events in Individual Phase 3 Trials

Table 55 details on-therapy hypoglycemic events (through the primary endpoint) using the derived severity classification. In the monotherapy study (GLP112756) and as an add on to metformin (GLP112753), there were no severe hypoglycemic events and the incidence of documented symptomatic hypoglycemia was small (2%) and similar between albiglutide and placebo treated subjects. In combination with pioglitazone the incidence of severe and documented symptomatic hypoglycemic events were slightly higher in the albiglutide arm, although events numbers were small.

When used in combination with a sulfonylurea (GLP1127564 and GLP114179) albiglutide was more likely to cause documented symptomatic hypoglycemia than

without concomitant sulfonylurea use. The incidence of hypoglycemic events in the albiglutide arm was lower than active comparator (glargine and liraglutide).

**Table 54: P3-ISP: On-therapy Hypoglycemic Events Prior to Hyperglycemia Rescue by Background Insulin and/or SU Status Albiglutide versus All Comparators**

Description Category	With Insulin and/or SU				Without Insulin and/or SU			
	All comparators (N=1101)		Albiglutide (N=1210)		All Comparators (N=1183)		Albiglutide (N=906)	
	n (%)	# of events	n (%)	# of events	n (%)	# of events	n (%)	# of events
Any on-therapy hypoglycemic event	377 (34.2)	1680	331 (27.4)	1193	139 (11.7)	531	60 (6.6)	149
On-therapy hypoglycemic event density <sup>1</sup>		136.78		86.53		34.77		11.67
Severity								
Severe	7 (0.6)	8	5 (0.4)	6	1 (0.1)	1	2 (0.2)	2
Documented symptomatic	285 (25.9)	1241	227 (18.8)	881	88 (7.4)	366	21 (2.3)	31
Asymptomatic	87 (7.9)	177	90 (7.4)	139	19 (1.6)	28	10 (1.1)	13
Probable symptomatic	55 (5.0)	92	48 (4.0)	86	36 (3.0)	55	20 (2.2)	37
Relative	63 (5.7)	136	36 (3.0)	70	33 (2.8)	79	21 (2.3)	66
Not applicable	5 (0.5)	8	4 (0.3)	10	2 (0.2)	2	0	0
Missing	2 (0.2)	18	1 (0.1)	1	-	-	-	-
Serious adverse event <sup>2</sup>								
Yes	3 (0.3)	3	0	0	1 (0.1)	1	0	0
No	374 (34.0)	1677	331 (27.4)	1193	138 (11.7)	530	60 (6.6)	149
Withdrawn due to hypoglycemic event								
Yes	2 (0.2)	2	1 (0.1)	1	1 (0.1)	1	1 (0.1)	1
No	375 (34.1)	1678	330 (27.3)	1192	138 (11.7)	530	59 (6.5)	148

ISS table 110 page 334 Source Data: Table SP3-26.18.1. SU = sulfonylurea.

Note: On-therapy events 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. On-therapy events prior to hyperglycemia rescue that were flagged by the investigator as hypoglycemic events are presented in this summary. Subjects with more than 1 hypoglycemic event were counted in all categories reported except as noted in footnote 2 below. Percentages were based on the number of subjects in each treatment grouping for the subgroup category presented.

1. The hypoglycemic adverse event (AE) incidence density per person-year = (number of hypoglycemic AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the on-therapy treatment period for the subgroup category presented.

2. Subjects with more than 1 hypoglycemic event are counted only once in the worst category.

**Table 55: Derived Severity of On-therapy Hypoglycemic Events Prior to Hyperglycemia Rescue Through the Primary Endpoint Using Associated Glucose Levels and ADA Definition by Study-level Treatment Groups (Phase 3 Integrated Safety Population)**

Study Number	Treatment	N / Total Exposure (years)	Any On-therapy		Severe		Documented Symptomatic	
			n (%)	Number of Events	n (%)	Number of Events	n (%)	Number of Events
GLP108486	Albiglutide	285 / 143.52	70 (24.6%)	188	0	0	45 (15.8)	134
	Pre-prandial lispro insulin	281 / 139.35	107 (38.1%)	430	2 (0.7)	2	84 (29.9)	325
GLP112753	Albiglutide	302 / 457.16	22 (7.3%)	66	0	0	9 (3.0)	12
	Sitagliptin	302 / 432.13	14 (4.6%)	31	0	0	5 (1.7)	12
	Glimepiride	307 / 456.67	76 (24.8%)	368	0	0	55 (17.9)	277
	Placebo	101 / 111.49	9 (8.9%)	14	0	0	4 (4.0)	4
GLP112754	Albiglutide	504 / 461.22	127 (25.2%)	127	2 (0.4)	2	86 (17.1)	277
	With sulfonylurea	413 / 380.82	123 (29.8%)	399	2 (0.5)	2	85 (20.6)	272
	Without sulfonylurea	91 / 80.40	4 (4.4%)	12	0	0	1 (1.1)	5
	Insulin glargine	241 / 225.03	89 (36.9%)	360	1 (0.4)	2	64 (26.6)	256
	With sulfonylurea	196 / 182.43	78 (39.8%)	340	1 (0.5)	2	56 (28.6)	242
	Without sulfonylurea	45 / 42.60	11 (24.4%)	20	0	0	8 (17.8)	14
GLP112755	Albiglutide 30 mg	150 / 139.70	11 (7.3%)	35	2 (1.3)	2	5 (3.3)	6
	Placebo	151 / 111.19	6 (4.0%)	14	0	0	2 (1.3)	5
GLP112756	Albiglutide 30 mg	101 / 95.12	6 (5.9%)	6	0	0	2 (2.0)	2
	Albiglutide 50 mg	99 / 89.17	6 (6.1%)	6	0	0	0	0
	Placebo	101 / 70.77	4 (4.0%)	4	0	0	2 (2.0)	2
GLP112757	Albiglutide	271 / 252.75	57 (21.0%)	176	1 (0.4)	2	36 (13.3)	127
	Pioglitazone	277 / 259.43	87 (31.4%)	322	3 (1.1)	3	68 (24.5)	236
	Placebo	115 / 84.26	13 (11.3%)	43	0	0	8 (7.0)	29
	Albiglutide	404 / 260.66	65 (16.1%)	196	0	0	42 (10.4)	142

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GLP114179	With sulfonylurea	241 / 157.11	60 (24.9%)	189	0	0	40 (16.6)	139
	Without sulfonylurea	163 / 103.55	5 (3.1%)	7	0	0	2 (1.2)	3
	Liraglutide	408 / 270.97	84 (20.6%)	211	0	0	54 (13.2)	125
	With sulfonylurea	232 / 153.11	72 (31.0%)	185	0	0	47 (20.3)	112
	Without sulfonylurea	176 / 117.86	12 (6.8%)	26	0	0	7 (4.0)	13

Source Data. ISS table 107 page 324 and SCS table 41 137, IAS Table SP3-26.21.1, IAS Table SP3-26.21.2, and Study GLP114130 Table 14.3.1-2.1.17 and Table 14.3.1-2.1.18

Note: the primary endpoint was assessed at Week 26 in Study GLP108486 and GLP114130, Week 32 in Study GLP114179, Week 52 in Studies GLP112754, GLP112755, GLP112756, and GLP112757, and Week 104 in Study GLP112753. On-therapy events 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. On-therapy adverse events (AEs) occurring prior to hyperglycemia rescue that were flagged by the investigator as hypoglycemic events and met the American Diabetes Association guidelines for categorization are presented in this summary. Subjects with more than one hypoglycemic event were counted in all severity categories reported. Percentages are based on the number of subjects in each treatment group for the study being summarized.

1. The hypoglycemic AE density per 100 person-years =  $100 * (\text{number of hypoglycemic AEs} / \text{person-years})$ , where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the treatment period being summarized.

2. Severity was derived using the American Diabetes Association guidelines for categorization of hypoglycemic events as follows: Severe = required assistance of another person; Documented symptomatic = typical symptoms accompanied by a plasma glucose concentration (PGC) of  $\leq 3.9$  mmol/L; and Asymptomatic = no symptoms but PGC  $\geq 3.9$  mmol/L.

#### 4MSU HYPOGLYCEMIC EVENTS

During the safety update there were no additional severe hypoglycemic events, SAEs or subjects withdrawn for hypoglycemia in the albiglutide group. The total number of severe hypoglycemic events has remained the same for the albiglutide group and increased in the all comparator group (8 events in 7 albiglutide-treated subjects and 10 events in 9 all comparator-treated subjects). SAEs remained the same in both treatment groups. Hypoglycemic events occurred more frequently in the albiglutide arm when given in combination with insulin or sulfonylurea. Data regarding hypoglycemic events received with the 4MSU was supportive of data submitted with the original BLA submission and is detailed in Table 56.

**Table 56: Summary of Incremental On-Therapy Hypoglycemic Events Prior to Hyperglycemic Rescue by Study (Derived Severity) Safety Population**

Study Number	Treatment	N <sup>1</sup>	Total Number events		Severe		Documented Symptomatic	
			n (%)	Number of Events	n (%)	Number of Events	n (%)	Number of Events
GLP112753	Albiglutide	302	4 (1.3)	9	0	0	0	0
	Sitagliptin	302	5 (1.7)	5	0	0	1 (0.3)	1
	Glimepiride	307	28 (9.1)	75	0	0	14 (4.6)	54
	Placebo	101	0	0	0	0	0	0
GLP112754	Albiglutide	504	33 (6.5)	63	0	0	7 (1.4)	29
	With sulfonylurea	414	32 (7.7)	62	0	0	7 (1.7)	29
	Without sulfonylurea	90	1 (1.1)	1	0	0	0	0
	Insulin glargine	241	28 (11.6)	89	1 (0.4)	1	10 (4.1)	64
	With sulfonylurea	197	25 (12.7)	86	1 (0.5)	1	9 (4.6)	63
	Without sulfonylurea	43	3 (7.0)	3	0	0	1 (2.3)	1
GLP112755	Albiglutide 30 mg	150	1 (0.7)	1	0	0	1 (0.7)	1
	Placebo	151	1 (0.7)	1	0	0	0	0
GLP112756	Albiglutide 30 mg	101	0	0	0	0	0	0
	Albiglutide 50 mg	99	0	0	0	0	0	0
	Placebo	101	0	0	0	0	0	0
GLP112757	Albiglutide	271	29 (10.7)	69	0	0	10 (3.7)	40
	Pioglitazone	277	28 (10.1)	41	0	0	7 (2.5)	8
	Placebo	115	5 (4.3)	11	0	0	2 (1.7)	8

Source Data: 120 day safety update Table 14 page 74

The 5 ongoing Phase III studies include the following: GLP112753, GLP112754, GLP112755, GLP112756, and GLP112757)

Note: On-therapy events 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. This summary presents pre-rescue, on-therapy events that were flagged by the investigator as hypoglycemic events and met the American Diabetes Association (ADA) guidelines for categorization. Percentages are based on the number of subjects in each treatment group for the subgroup category presented. Subjects with more than 1 hypoglycemic event were counted in all severity and intervention categories reported. A severe event may have had more than 1 intervention reported. Severity was derived using the ADA guidelines for categorization of hypoglycemic events.

## RENAL STUDY (GLP114130) HYPOGLYCEMIC EVENTS

The proportion of subjects with on-therapy pre-rescue hypoglycemia was higher in the albiglutide treatment group [23.7% (59/ 249 subjects, 133 events)] compared with the sitagliptin treatment group [14.2% (35/246 subjects, 118 events)].

Severe hypoglycemic events occurred in 0.4% (1 subject, 1 event) in the albiglutide treatment group and 0.8% (2 subjects, 2 events) in the sitagliptin treatment group. All severe events occurred in subjects taking background SU therapy.

### Hypoglycemic Events with Sulfonylurea use (Renal Study)

When used in combination with a sulfonylurea albiglutide was more likely to cause documented symptomatic hypoglycemia. Approximately 15% (25/167 subjects with 46 events) receiving albiglutide + SU experienced a hypoglycemic event vs. 1.2 % (2/82 subjects, 2 events) of subject on albiglutide without SU.

**Table 57: Derived Severity of On-therapy Hypoglycemic Events Before Hyperglycemia Rescue Using Associated Glucose Levels and American Diabetes Association Definitions Through the Time of the Primary Endpoint (Study GLP114130)**

Treatment	N <sup>1</sup>	Total Number events		Severe		Documented Symptomatic	
		n (%)	Number of Events	n (%)	Number of Events	n (%)	Number of Events
Albiglutide	249	51 (20.5%)	98	0	0	26 (10.4)	48
With sulfonylurea	167	48 (28.7%)	93	0	0	25 (15.0)	46
Without sulfonylurea	82	3 (3.7%)	5	0	0	1 (1.2)	2
Sitagliptin	246	33 (13.4%)	108	2 (0.8)	2	14 (5.7)	30
With sulfonylurea	173	30 (17.3%)	103	2 (1.2)	2	14 (8.1)	30 /
Without sulfonylurea	73	3 (4.1%)	5	0	0	0	0

Source: SCS Table 41, Page 137

### Hypoglycemic events by renal impairment categories (Renal Study)

A higher proportion of subjects with moderate renal impairment (n=30, 29.4%) and severe renal impairment (n=8, 42.1%) experienced a hypoglycemic event compared to subjects with mild renal impairment (n=22, 17.2%).

**Reviewer Comment: Conclusion regarding hypoglycemic events and severity of renal impairment is limited by the small sample size.**

## GASTROINTESTINAL EVENTS

The primary review of albiglutide’s gastrointestinal adverse event profile focuses on albiglutide and placebo comparison treatment groupings, as active comparators had differing gastrointestinal adverse event profiles which could confound interpretation of the data. A higher incidence of gastrointestinal adverse events occurred in subjects treated with albiglutide vs. placebo (38.8% vs. 33.1%, respectively). AEs occurring in >5% of subjects that were numerically higher in the albiglutide group were events of diarrhea and nausea. These events generally occurred within the first 26 weeks of treatment and were primarily mild in intensity and resolved within a week.

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

Gastrointestinal (GI) adverse events occurring in  $\geq 5\%$  subjects across treatment groups are summarized in Table 58.

**Table 58: P3-ISP: On-therapy Adverse Events in the Gastrointestinal Disorders System Organ Class Occurring in More Than 5% of Subjects in Either Treatment Group**

	Albiglutide vs. All Comparators				Albiglutide vs. Placebo			
	All Comparators		Albiglutide		Placebo		Albiglutide	
	(N=2284)		(N=2116)		(N=468)		(N=923)	
	n (%)	Number of AEs / Density <sup>1</sup>	n (%)	Number of AEs / Density <sup>1</sup>	n (%)	Number of AEs / Density <sup>1</sup>	n (%)	Number of AEs / Density <sup>1</sup>
<b>Gastrointestinal disorders</b>								
Any event	732 (32.0)	1374/37.87	806 (38.1)	1663/49.35	155(33.1)	291/34.61	358 (38.8)	737/41.07
Diarrhea	209 (9.2)	273 / 7.52	272 (12.9)	374 / 11.10	49 (10.5)	62 / 7.37	121 (13.1)	168 / 9.36
Nausea	242 (10.6)	283 / 7.80	243 (11.5)	351 / 10.42	45 (9.6)	53 / 6.30	102 (11.1)	145 / 8.08
Vomiting	101 (4.4)	117 / 3.22	104 (4.9)	147 / 4.36	12 (2.6)	12 / 1.43	39 (4.2)	52 / 2.90
Constipation	87 (3.8)	96 / 2.65	100 (4.7)	108 / 3.21	24 (5.1)	28 / 3.33	42 (4.6)	46 / 2.56

Source Data: SCS Modified from Table 50, Page 159.

1. Number of adverse events (AEs) = the total number of AEs at each level of summarization. Density per 100 person-years = 100 \* (number of AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the treatment period being summarized.

### Albiglutide vs. Placebo

Overall, a greater number of subjects had gastrointestinal events when treated with albiglutide vs. placebo (38.8% vs. 33.1%, respectively). AEs occurring in >5% of subjects that were numerically higher in the albiglutide group were events of diarrhea and nausea.

### *Diarrhea*

Cases of diarrhea were generally mild in intensity in the albiglutide arm (60.3%, 73/121 subjects) with approximately 5% (6/121 subjects) experiencing severe episodes. There were no SAEs of diarrhea and a greater number of subjects withdrew from the placebo arm for diarrhea (6.1%, 3/49 subjects) vs. albiglutide (3.3%, 4/121). Diarrhea resolved within 1 week in 64.3% of albiglutide treated subjects and 56.5% of placebo subjects.

### *Nausea*

Subjects experiencing nausea generally experienced mild episodes in the albiglutide arm (65.7%, 67/102) as well as the placebo group (73.3%, 33/45). There were no SAEs of nausea. A higher proportion of subjects in the placebo group (4.4%, 2/45) withdrew for nausea compared to subjects treated with albiglutide (2.9%, 3/102). Nausea resolved within 1 week in 60.0% of albiglutide subjects and 52.8% of placebo subjects.

### *Vomiting*

The proportion of subjects with vomiting was 4.2% (39 subjects) in the albiglutide group compared with 2.6% (12 subjects) in the placebo group. Severe vomiting was higher in albiglutide compared to placebo (10.3 vs. 8.3%, respectively).

Review of preferred terms adverse events under the gastrointestinal disorders SOC revealed 2 single event terms of **projectile vomiting** and **retching**, which were not included in the sum of vomiting events described above. These 2 events did not occur in placebo treated subjects.

Subject 3550753986: 63-year old male experienced mild **flushing** on the same day of the first dose of investigational product. On study day 21 the subject experienced severe **projectile vomiting** resulting in study drug discontinuation

***Reviewer Comment: The applicant was asked to provide narrative information for events of “retching”. One case of retching occurred on study day 252 and was described as “dry heaves”. Another subject experienced nausea and retching and the investigator concluded a possible relationship to study medication. Neither event resulted in study drug withdrawal, and a temporal association to albiglutide administration was not apparent from narrative review. The preferred term of projectile vomiting should be added to the sum of vomiting events under albiglutide.***

Additional adverse events not in favor of albiglutide compared to placebo that occurred in >2% of subjects were events of gastroesophageal reflux disease (3.5 vs. 1.9%) and dyspepsia (3.4 vs. 2.8%).

The majority of subjects in each treatment arm who experienced a GI AE experienced the event within the first 26 weeks (69%, 246/358 albiglutide-treated vs. 63%, 97/155 placebo-treated subjects).

### Gastrointestinal serious adverse events

As detailed in Table 59 there was a slightly higher incidence of GI SAEs in the albiglutide group compared to placebo. SAEs occurring in 2 subjects in the albiglutide group were events of abdominal hernia, colitis, gastritis, vomiting, small bowel obstruction and pancreatitis. .

**Table 59: On-therapy Serious Gastrointestinal Adverse Events with a Higher Number in the Albiglutide Group (Albiglutide vs. Placebo).**

	Placebo (N=468)		Albiglutide (N=923)	
	n (%)	Number of AEs	n (%)	Number of AEs
<b>Any GI event</b>	6 (1.3)	6	16 (1.7)	18
Abdominal hernia	0	0	2 (0.2)	2
Colitis ischemic	0	0	2 (0.2)	2
Gastritis	0	0	2 (0.2)	2
Pancreatitis	0	0	2 (0.2)	2
Small intestinal obstruction	0	0	2 (0.2)	3
Vomiting	0	0	2 (0.2)	2
Constipation	0	0	1 (0.1)	1
Gastroesophageal reflux	0	0	1 (0.1)	1
Lower GI Hemorrhage	0	0	1 (0.1)	1
Pancreatitis acute	0	0	1 (0.1)	1
Sigmoiditis	0	0	1 (0.1)	1

ISS Table SP3-29.1.2 and Table 139 page 456. (Placebo arm studies GLP112753, GLP112755, GLP112756, and GLP112757).

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

SAE narratives were reviewed for vomiting events are described below.

Subject 3570756987: 61 year old man with a history of chronic constipation, experienced **vomiting** up to 20x /day on study day 112 requiring hospitalization. The event occurred 3 weeks after up-titration to 50 mg of albiglutide. An abdominal X-ray was negative for obstruction and he was treated with IV fluids and antiemetics in the hospital. Study medication was held and upon resumption of study drug the subject experienced mild emesis resulting in study discontinuation on day 146.

***Reviewer Comment: The temporal relationship of vomiting to readministration of study drug suggests a possibility of relatedness to the higher dose of drug product.***

Subject 7969757986: 50 year old female developed vomiting while on vacation requiring hospitalization on study day 165. The subject developed nausea and **vomiting** with no other focal signs and she was unable to tolerate anything. She was admitted to the hospital and was afebrile with no abdominal pain throughout her hospital stay. The subject received metoclopramide, and physiological electrolyte solution for treatment for this event. Study medication was continued without additional events of vomiting.

*Review of event narratives for serious inflammatory gastrointestinal events was conducted to identify a safety concern for inflammation or bleeding events. These narratives are briefly described below.*

Subject 3579756989: 49 year old female with arthritis developed rectal bleeding on study day 367. Colonoscopy demonstrated **ischemic colitis** with diverticulosis and biopsy results showed no specific histopathology. The subject took aspirin daily and naproxen as needed for headaches.

Subject 3660753986: 67 year old female with a history of ischemic heart disease and hypertension developed a lower GI bleed on study day 127. The subject was diagnosed with **ischemic colitis**.

Subject 3504754996: 69 year old female with a past history of coronary artery disease (on plavix and aspirin) developed a **lower gastrointestinal hemorrhage** on study day 331. The event occurred after the patient underwent a colonoscopy and had a cecal polyp removed.

Subject 3569757986: 59 year old female with history of diverticulitis and hypertension developed **sigmoiditis** on study day 75.

*An additional search for the preferred terms of gastrointestinal bleed or ulcer was conducted.*

Subject 3412754986: 79 year old man with a history of gastroesophageal reflux, heart disease on plavix and aspirin developed a **gastrointestinal bleed** 1100 days after study initiation, with colonoscopy showing diverticulitis

Subject 3309130011: 55 year old female with a history of hypertension, dyspepsia and dyslipidemia develop mild dermatitis on study day 71 and on study day 308 developed melena and was found to have **gastric ulcers**.

***Reviewer Comment: The etiology of inflammatory and bleeding events are confounded by subject risk factors of age, underlying co-morbidities and concomitant medications which can potentiate the development of colitis and bleeding.***

Review of serious events of small bowel obstruction are described below.

Subject 3455753980: 58 year old female with a history of small intestine obstruction and abdominal surgery with associated abdominal adhesions developed **small bowel obstruction** on study day 37 and 53, resulting in poor oral intake and hospitalization. Radiographic imaging revealed small bowel obstruction on both occasions. The subject was treated with nasogastric tube insertion.

***Reviewer Comment: The subject had adhesions which are risk factors for the development of obstruction.***

Subject 3609757982: 62 year old male with a history of hypertension and dyslipidemia presents on study day 5 with dyspepsia, diarrhea and abdominal distention. The subject was unable to eat and was hospitalized. A small bowel series revealed normal transit time and was not suggestive of obstruction. Symptoms were attributed to expected gastrointestinal effects of the investigational product. Discharge diagnoses were gastroenteritis and ileus based on results of abnormal CT scan.

***Reviewer Comment: Review of narratives for serious cases of small bowel obstruction (described above) and events of abdomen hernia and gastritis did not suggest an additional safety concern.***

### **Gastrointestinal Withdrawals**

Overall withdrawals due to GI AEs were similar among albiglutide and placebo treated subjects [1.7%, (8/423 placebo and 16/923 albiglutide)]. Withdrawal due to events of pancreatitis (0.3%, vs. 0) and vomiting (0.3%, vs. 0) were higher in the albiglutide group compared to placebo.

### **Renal impairment in the setting of GI adverse events**

GLP-1 agonists have been associated with severe nausea, vomiting and diarrhea resulting in dehydration leading to altered renal function. As a result the applicant reviewed the high level term (HLT) renal impairment in the P3-ISP to determine if there were overlapping GI events at the time the subject developed renal impairment that could have precipitated a decline in renal function.

*An information request sent to the sponsor clarified that the criteria used to identify “overlapping GI events” included any concurrent GI event or a GI event occurring within*

*2 weeks prior to the renal impairment event. However the gastrointestinal (GI) adverse events represented only GI adverse events from the Gastrointestinal disorders SOC and not gastrointestinal-related adverse events from infectious etiologies*

- In the P3-ISP comparing albiglutide vs. all comparators, 32 subjects reported adverse events with a HLT of renal impairment (14 albiglutide-treated subjects vs. 18 in the all comparators group).
- The applicant states that 5 of 14 subjects in the albiglutide group had GI AEs around the time of the AE of renal impairment. These events were non-serious, mild or moderate intensity and did not result in study drug withdrawal

Narratives for subjects experiencing adverse events of renal impairment with a temporal relationship to a GI event at the time of the renal event are detailed below.

Subject 1280486002: 55 year old female with a history of hypertension and a kidney stone developed acute renal failure in the setting of **gastroenteritis** on study day 354. The subject presented to the emergency room with a 4 day history of nausea, vomiting, diarrhea and dehydration and was found to be hypotensive (blood pressure 74/54 mm/hg) and have acute renal impairment (creatinine 1.43 mg/dL, local lab ref: 0.7-1.2 mg/dl) and BUN 26 g/dL ( ref: 7-18 g/dL). At baseline the subject did not have renal insufficiency (central lab creatinine 53 (ref 44-124 umol/L). Stool and urine cultures were negative. Chest and abdominal x-ray and head CT did not reveal any acute process. Temperature not provided.

Subject 3582754987: 54 year old male experienced acute renal failure (creatinine 2.6 mg/dL, reference range: 0.7- 1.3 mg/dL) resulting in hospitalization. The subject had nausea, gastric burning and headache at the time of the event and received IV fluids for treatment of renal failure. Renal and abdominal ultrasounds were negative for pathology. No action was taken with the study medication and the subject was discharged with the event of renal failure was considered resolved. The subject did not experience subsequent renal or GI AEs

Subject 3669754983: 55 year old man experienced a CVA on study day 298 and per the narrative the subject developed acute renal failure and had constipation at that time.

Subject 1257486005: 65 year old developed myocardial infarction on study day 142 and subsequent palatal edema and acute renal failure.

Subject 3716754986: 77 year old male developed nausea and acute renal failure on study day 838 in the setting of cellulitis. There was also a non-obstructing 4 mm right renal lower pole stone.

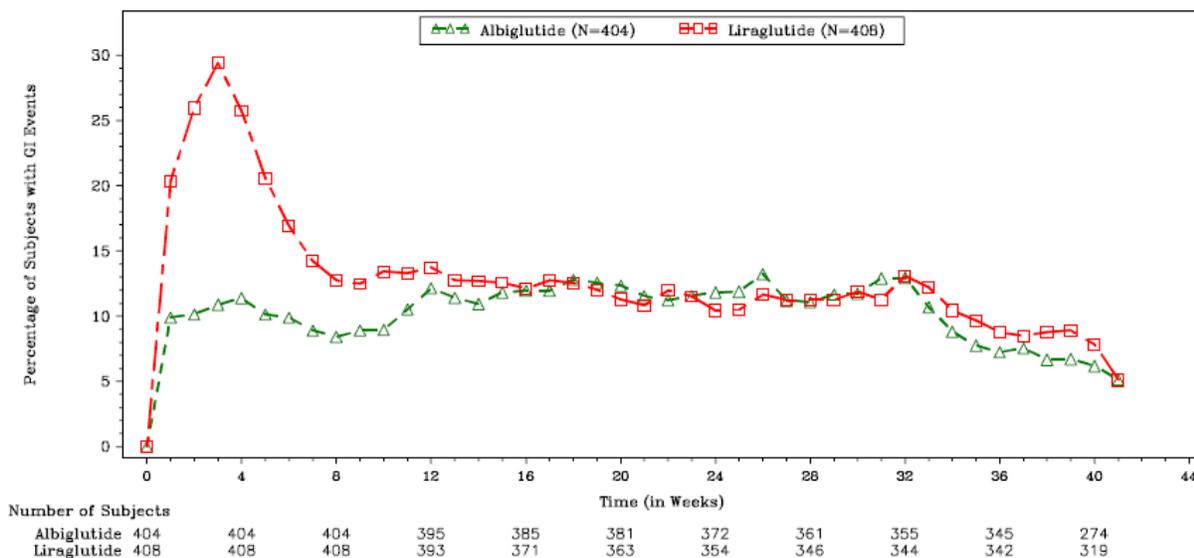
***Reviewer Comment: Many of the narratives lacked sufficient data to make an assessment of study drug causality. From the information provided a safety***

**signal for renal impairment resulting from gastrointestinal events could not be established. Events of diarrhea, nausea and vomiting are the most common adverse gastrointestinal events noted with albiglutide treatment. Similar GI adverse events with other GLP-1 agonists have resulted in dehydration and hypovolemia with a subsequent renal failure. Therefore the relationship between albiglutide related gastrointestinal adverse events and the development of renal failure should be investigated further as an adverse event of interest in the CV outcomes study and monitored post marketing.**

STUDY GLP114179: Albiglutide vs. Liraglutide

Study GLP114179 compared albiglutide to the GLP-1 agonist liraglutide. A greater proportion of on-therapy AEs in the GI Disorders SOC occurred in the liraglutide treatment group (49.0%, 200/408 subjects) compared to albiglutide treatment (35.9%, 145/ 404 subjects). The incidence of nausea was higher in the liraglutide treatment group (29.2%) compared to albiglutide treated subjects (9.9%). Vomiting was reported in a lower proportion of subjects in the albiglutide group (5.0%) compared to the liraglutide group (9.3%). The incidence of diarrhea was similar in both groups (14.9% in albiglutide and 13.5% in placebo). The largest difference in GI events between the treatment arms occurred in the first 12 weeks as depicted in Figure 8 .

**Figure 8: On-therapy Gastrointestinal Events Over Ttime (Study GLP114179).**



Note: On-therapy events are those that have a start date on or after the first day of study medication and within 56 days after the end of study medication. This figure presents on-therapy events coded to the gastrointestinal disorders system organ class. The denominator used for percentages is the number of subjects (as shown above) considered on therapy for that particular timepoint. An event may be counted in multiple weeks depending on its duration. If a subject experienced more than one GI adverse event within a week, the subject is counted only once. All percentages of events beyond Week 40 are based on the small number of subjects who have on-therapy periods that extend beyond the protocol expected 40 week duration.

Source CSR- GLP114179 Figure 14.3.1-2.2.1 Page 2999

While there were no SAEs in the albiglutide group, 0.7% (3 subjects) reported a SAE in the liraglutide group. Adverse events in the GI Disorders SOC leading to withdrawal of active treatment were also more common in the liraglutide group (6.4%) compared to the albiglutide group (2.5%). In addition 2.2 % (9 subjects) discontinued liraglutide-treatment due to nausea compared with 0.5% (2 subjects) treated with albiglutide.

**Reviewer Comment: The proportion of subjects having nausea and vomiting was lower in the albiglutide group versus the liraglutide group while the incidence of diarrhea was similar between groups. However conclusions regarding safety are limited by the open label design of the study.**

#### 4MSU GASTROINTESTINAL EVENTS

As previously noted the primary review of gastrointestinal adverse events focused on albiglutide vs. placebo treated subjects since active comparators had differing gastrointestinal adverse event profiles. The update provided data comparing albiglutide to all comparators

During the incremental period overall GI adverse events were similar between albiglutide and all comparators (7.3, 104/1427 vs. 7.1%, 113/1595 respectively). The most frequent reported GI events in albiglutide vs. all comparators were events of diarrhea (2%, 29/1427 vs. 1.5%, and 24/1595 in comparators) and nausea (1.1%, 15/1497 vs. 1.3%, and 20/1595 in comparators). A similar proportion of subjects 0.3% (3 subjects in each group) experienced SAEs and 1 subject in each treatment comparison grouping withdrew for a GI adverse events.

#### CUMULATIVE GASTROINTESTINAL EVENTS

Data through the safety update demonstrated that 40% (845/2116) of albiglutide and 34.1% (779/2284) of all comparators experienced a GI AE. Gastrointestinal AEs occurring in  $\geq 5\%$  subjects in the albiglutide arm were events of diarrhea (13.7%, 289/2116 vs. 9.9%, 22/2284 in comparators), nausea (12%, 253/2116 vs. 11.3%, 258/2284 in comparators), vomiting (5.2, 115/2116 vs. 4.7%, 108/2284 in comparators) and constipation (5%, 105/2116 vs. 4%, 92/2284 in comparators). The highest numeric imbalance between albiglutide and comparators were for events of diarrhea.

Review of the cumulative GI event data also demonstrated that a higher incidence of periodontal disease in albiglutide treated subjects compared to all comparators (0.2%, 4 subjects vs. 0).

**Reviewer Comment: The applicant was asked to provide clinical information regarding cases of periodontal disease. Review of narratives revealed event onset dates ranging from study day 73 to 1003. In half the cases the investigator**

**determined that the periodontal disease may have been caused by the investigational product. An etiologic relationship to study drug was limited by a lack of information regarding relevant risk factors for developing periodontal disease.**

#### RENAL STUDY (GLP114130) GASTROINTESTINAL EVENTS

On-therapy GI AEs occurred with a higher incidence and higher event rate in the albiglutide treatment group (31.7%, 79/249 of subjects) compared with the sitagliptin group (25.2%, 62/246 of subjects). Diarrhea (10%, 25/249 vs. 6.5%, 16/246) and constipation (6%, 15/249 vs. 2.4%, 6/246) occurred more frequently in the albiglutide group vs. sitagliptin. Worsening of renal impairment due to GI intolerance did not occur in the albiglutide group.

Overall, in the albiglutide arm subjects with mild renal impairment reported the lowest proportion of any GI events compared with moderate and severe renal impairment. In the albiglutide group the incidence of diarrhea, nausea and vomiting events increased with worsening renal impairment. Four subjects in the albiglutide group (all with moderate renal impairment) and 1 subject in the sitagliptin group with (mild renal impairment) withdrew from the study due to a GI events.

**Table 60: On-Therapy Gastrointestinal Adverse Events Occurring in More Than 2 Subjects in Either Treatment Group Presented by Renal Impairment Severity (Safety Population)**

	Sitagliptin			Albiglutide		
	Mild (N=128)	Moderate (N=101)	Severe (N=17)	Mild (N=128)	Moderat (N=102)	Severe (N=19)
	n (%)	n (%)	n (%)	N (%)	n (%)	n (%)
Gastrointestinal disorders						
Any event	38 (29.7)	20 (19.8)	4 (23.5)	35 (27.3)	35 (34.3)	9 (47.4)
Diarrhoea	10 (7.8)	5 (5.0)	1 (5.9)	8 (6.3)	13 (12.7)	4 (21.1)
Constipation	5 (3.9)	1 (1.0)	0	7 (5.5)	6 (5.9)	2 (10.5)
Nausea	4 (3.1)	3 (3.0)	1 (5.9)	4 (3.1)	5 (4.9)	3 (15.8)
Dyspepsia	5 (3.9)	3 (3.0)	1 (5.9)	2 (1.6)	3 (2.9)	0
Gastritis	4 (3.1)	3 (3.0)	0	2 (1.6)	2 (2.0)	1 (5.3)
Gastroesophageal reflux disease	5 (3.9)	1 (1.0)	1 (5.9)	1 (0.8)	1 (1.0)	1 (5.3)
Haemorrhoids	3 (2.3)	0	0	4 (3.1)	1 (1.0)	1 (5.3)
Vomiting	2 (1.6)	1 (1.0)	0	1 (0.8)	2 (2.0)	1 (5.3)
Abdominal discomfort	2 (1.6)	1 (1.0)	0	2 (1.6)	0	1 (5.3)

Abdominal pain upper	3 (2.3)	0	0	1 (0.8)	1 (1.0)	0
Flatulence	1 (0.8)	0	0	0	3 (2.9)	1 (5.3)
Abdominal	0	1 (1.0)	0	1 (0.8)	0	2 (10.5)
Abdominal hernia	1 (0.8)	1 (1.0)	1 (5.9)	0	1 (1.0)	0
Gastric ulcer	1 (0.8)	0	0	0	3 (2.9)	0

Source Data: Table 14.3.1-2.2.1.1. CSR GLP114130 (b) (6) 66, Page 210.

AE = adverse event.

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. 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. The preferred terms within the gastrointestinal disorders system organ class are presented by decreasing frequency of incidence for both treatment groups combined.

1. Number of AEs = 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.

## IMMUNOGENICITY

The integrated clinical immunogenicity report was reviewed for evaluation of albiglutide antibody formation. Approximately 4.4 % of subjects across the clinical program who received at least one dose of albiglutide developed treatment emergent albiglutide antibodies. In the P3-ISP, 5.1% of subjects developed antibodies after initiation of treatment. The majority of subjects developed antibodies during the first 26 weeks of treatment and 62% of antibody positive subjects had only 1 or 2 positive test results. Overall serious adverse event rates occurred at similar frequencies in antibody positive and negative subjects. Immunogenicity related adverse events of special interest evaluated in the albiglutide clinical program were injection site reactions (ISRs) and systemic allergic reaction (SARs). These events are discussed separately in section 7.3.5.6 and 7.3.5.7.

Albiglutide is a fusion protein of GLP-1 and human albumin. As noted in Dr. Wange's review the presence of human albumin sequence in the fusion protein resulted in albiglutide being highly immunogenic in animals. In mice, the antidrug antibody (ADA) response caused diminished exposure to albiglutide and was associated with type 3 hypersensitivity reactions (immune complex deposition) in a subset of animals. Due to the biologic properties of albiglutide immunogenicity was identified as an adverse event of special interest.

Immunogenicity was evaluated in 2934 albiglutide treated subjects in 15 clinical studies (8 Phase III, 2 Phase IIb, and 5 Phase I/IIa studies). Samples were collected at regular 12-week interval the first year and 24 week intervals during the second and third year of treatment. An 8-week follow-up period was included in all immunogenicity studies for subjects who had completed or withdrawn from the study. In the Phase III studies,

antibody measurements were not conducted for subjects receiving placebo or comparator treatments (except in study GLP112756 -all subjects were tested for antibodies).

A subset of subjects in Study GLP112754 and Study GLP112756 were switched from Process 2 to Process 3-derived albiglutide product during the third year of treatment (primary endpoint for both studies was at Week 52). For these 2 “switch” studies, additional immunogenicity samples were collected at Week 116 and Week 142, reducing the sampling interval from every 24 to every 12 weeks.

### Testing Strategy

Immunogenicity testing followed a tiered-testing approach. Subjects who had positive anti-albiglutide antibodies were tested for cross reactivity to GLP-1, human albumin, glucagon, and anti-albiglutide and anti-GLP-1 neutralizing activity. In addition anti-albiglutide IgE testing was performed for any investigator identified allergic reaction. Subjects were considered antibody positive if at least 1 post dose sample tested positive for anti-albiglutide antibodies

### Clinical Immunogenicity Results – (P1-P3)

- 2934 subjects received at least one dose of study drug across the clinical program
  - 18/2934 subjects (0.6%) of albiglutide-treated subjects tested positive for albiglutide reactive antibodies at baseline. Six of these subjects did not have a positive post-baseline value.
  - 128/2934 subjects (4.4%) developed treatment-emergent anti-albiglutide antibodies after at least one dose.

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

### Clinical Immunogenicity Results – (P3-ISP)

Due to the low incidence of immunogenicity in the overall population (<5%) the applicant pooled data from 7 P3 studies (GLP108486, GLP114179, GLP112754, GLP112755, GLP112756, GLP112757, and GLP112753) to evaluate the clinical impact of antibody formation on efficacy and safety. This analysis involved 2098 albiglutide-treated T2DM subjects.

- 116/2098 subjects (5.5%) tested positive for at least 1 post baseline anti-albiglutide antibody
  - 9/116 had preexisting anti-albiglutide antibodies at baseline
- 107/2098 subjects (5.1%) developed treatment-emergent antibodies at varying times after initiation of treatment

- 75 subjects tested positive for antibodies by week 26

The applicant reviewed duration of antibody positivity using data from the 5 long-term ongoing 3-year studies (GLP112753, GLP112754, GLP112755, GLP112756, and GLP112757).

- There were 53/ 85 subjects (62.4%) who tested positive at only 1 or 2 visits. The applicant described these as “transient responses” (antibodies lasting less than 24 weeks).
- Mean ( $\pm$ SD) baseline anti-albiglutide titers in antibody positive subjects in the P3-ISP were 298.4 $\pm$ 241.9. Mean antibody titers were 430 at week 26, and subsequently decreased to 247 and 236 at week 52 and 104, respectively.
- Anti-albiglutide IgE testing was performed for subjects experiencing an investigator identified potential systemic allergic reaction and there. There were no anti-albiglutide IgE antibodies detected in the program.
- Antibodies were generally non-neutralizing, except in 1 subject (Subject 8413179001) with pre-existing anti-albiglutide antibodies who tested weakly positive for albiglutide neutralizing antibodies. The neutralizing antibodies in this subject had no apparent clinical relevance (See Section 6).
- The applicant states that in most subjects, positive antibody status was transient and of low titer.
- The majority of anti-albiglutide positive subjects also tested positive for anti-GLP-1 (92/116) antibodies.
- 8 subjects had multiple positive anti-albumin antibody assessments. The applicant states that these subjects were reviewed for notable AEs (albumin levels, urinary albumin-to creatinine ratio, and eGFR, and there did not appear to be an effect on albumin levels or renal function).
- For the 3 subjects with anti-glucagon antibodies (Subjects 3674756980, 3796753988, and 7063753910) there were no AEs related to hypoglycemia

### **Serious adverse events in antibody positive subjects**

The proportion of SAEs was relatively balanced between antibody positive and negative subjects (12.9%, 15/116 vs. 11.4%, 220/1927 respectively). The most common SAE in anti-albiglutide antibody positive subjects occurred in the cardiac and nervous system disorders SOC (3.4%, 4/116). Most events were single events and there did not appear to be a consistent pattern. The applicant notes that SAEs relating to the immune system or allergic type reactions were not noted in antibody positive subjects. One SAE of asthma occurred in an antibody positive subject (0.9%) and 3 in antibody negative subjects (0.2%), and none of these events led to withdrawal of active treatment. The proportion of anti-albiglutide antibody positive subjects who discontinued treatment was similar to that for antibody negative subjects (23.1% vs. 27.3%).

Immunogenicity related adverse events of special interest evaluated in the albiglutide clinical program were injection site reactions (ISRs) and systemic allergic reaction (SARs). ISRs are discussed in section 7.3.5.6 and SARs are discussed 7.3.5.7. All 8 albiglutide-treated subjects who discontinued treatment for a potential SAR were anti-albiglutide antibody negative.

#### 4MSU IMMUNOGENICITY

There were no new subjects who tested positive for antibodies after the BLA submission. Three subjects continued to test positive for antibodies after the data cut off. There were no new ISRs or SARs reported for these subjects.

#### CUMULATIVE IMMUNOGENICITY

Overall 116/2098 (5.5%) of subjects on the P3-ISP had post baseline positive antibodies to albiglutide (9 were positive at baseline). Three subjects continued to test positive after the BLA submission and did not experience ISRs or SARs.

#### RENAL STUDY (Study GLP114130) IMMUNOGENICITY

Immunogenicity samples were collected at baseline, week 26 (primary endpoint), and week 60 (8-week follow-up).

- Anti-albiglutide antibodies developed in 2.6 % (6/231) of albiglutide-treated subjects. One additional subject had baseline positive antibodies.
- 5 subjects tested positive for anti–GLP-1 antibodies and 1 subject tested positive for anti-albumin antibodies. There was no reactivity with glucagon and there were no positive values for anti-albiglutide IgE antibodies.
- 5/6 subjects with treatment-emergent antibodies tested positive at week 26 and 3 subjects tested positive at week 60.
- Mean antibody titers ( $\pm$ SD) were 215 ( $\pm$ 134) at week 26 and 79 ( $\pm$ 51) at week 60.
- There were no SAEs or potential SARs reported for antibody-positive subjects. Of the 20 albiglutide-treated subjects with ISRs, one tested positive for anti-albiglutide antibodies.

#### **INJECTION SITE REACTIONS**

Review of injection site reactions was conducted in the P3-ISP by comparing albiglutide to placebo treated subjects. A higher proportion of subjects in the albiglutide treatment group experienced an injection site reaction compared with placebo treated subjects (17.6% vs. 7.5%). Events were more often reported within the first 26 weeks of study treatment. Compared to placebo a higher proportion of subjects experienced severe reactions (1.9 % vs. 0) and withdrew from treatment (2% vs. 0.2%). There were no

SAEs in either treatment group. Most subjects who had ISRs were anti-albiglutide antibody negative, although subjects who were antibody positive were more likely to have events.

Injection site reactions were identified by the investigator as either AEs with the PT 'injection site reaction' or other PTs that were classified by investigators as ISRs on the eCRF. Phase III studies specified the abdomen as the subcutaneous injection site. For each subject, the time to first occurrence of an ISR event was calculated as the number of days between the first dose date and the date of onset of the first on-therapy ISR event plus 1.

*Since the comparators in the P3-ISP included injectable therapies this review focused primarily on albiglutide compared to placebo and active injected comparators.*

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

#### Albiglutide vs. Placebo

As described in Table 61, a higher proportion of subjects in the albiglutide treatment group experienced an injection site reaction compared with placebo treated subjects (17.6% vs. 7.5%). These events were more often reported within the first 26 weeks of study treatment. While there were no severe reactions in the placebo group, 1.9% of albiglutide treated subjects experienced severe reactions. However, there were no SAEs in either treatment group. Median duration of ISRs was longer in the albiglutide group (7 vs. 2 days) and there was a greater proportion of withdrawals in the albiglutide treatment arm (2.0 vs. 0.2%), as well as reactions requiring treatment (6.3 % vs. 0.9%).

Among subjects who had ISRs, most had 1 or 2 events in the albiglutide group (61.7%, 100/162) and the placebo group (80%, 28/35). A higher proportion of subjects in the albiglutide group experienced >11 events (albiglutide 14.2% [23/162] vs. placebo 8.6% [3/35]) and a few subjects reported >20 events each (albiglutide 6.8% [11/162] vs. placebo 8.6% [3/35]). The applicant notes that a small number of subjects accounted for a large number of events; 23 subjects in the albiglutide group had approximately 620 events (12 subjects with 11 to 20 events plus 11 subjects with >20 events). The 23 albiglutide-treated subjects from the placebo comparison are a subset of the 38 subjects in the all comparators treatment comparison grouping experiencing the majority of ISRs. Details regarding ISRs in this group are provided below (Albiglutide vs. All Comparators).

**Table 61: On-therapy Injection Site Reaction Characteristics Overall - Albiglutide vs. Placebo (P3-ISP)**

	<b>Placebo</b>	<b>Albiglutide</b>
	<b>N=468</b>	<b>N=923</b>
	<b>n (%)</b>	<b>n (%)</b>
Subjects with Reactions	35 (7.5)	162 (17.6)
Subjects with Reactions at 52 Weeks	31 (6.6)	139 (15.1)
Subjects with Reactions at 26 Weeks	31 (6.6)	114 (12.4)
Subjects with SAEs	0	0
Subjects Withdrawn Due to the Event	1 (0.2)	18 (2.0)
Subjects Withdrawn Due to the Event at 52	0	15 (1.6)
Subjects Withdrawn Due to the Event at 26	0	10 (1.1)
Number of subjects who received treatment reaction	4 (0.9)	58 (6.3)
<b>Maximum intensity per subject</b>		
n	35	162
Mild	33 (94.3)	118 (72.8)
Moderate	2 (5.7)	41 (25.3)
Severe	0	3 (1.9)
<b>Number of events</b>	178	934
Duration of events (days)		
n	175	830
Median	2.0	7.0

Source: SCS Table 54 & 55 page 170 and 171

ISRs occurring in > 1% of subjects were associated with terms of injection site reaction, hematoma, erythema, rash and pruritus for albiglutide and terms of injection site reaction, erythema and pruritus for placebo (Table 62). Seven subjects in the albiglutide group had a preferred term of injection site hypersensitivity vs. none in the placebo arm placebo.

**Table 62: On-therapy Injection Site Reactions Occurring in More than 2 Subjects - Albiglutide vs. Placebo (P3-ISP)**

<b>System Organ Class Preferred Term</b>	<b>Placebo (N=468)</b>	<b>Albiglutide (N=923)</b>
	<b>n (%)</b>	<b>n (%)</b>
Any injection site reaction	35 (7.5)	162 (17.6)
<b>General Disorders and administration site</b>		
Any event	31 (6.6)	153 (16.6)
Injection site reaction	10 (2.1)	97 (10.5)
Injection site hematoma	9 (1.9)	19 (2.1)
Injection site erythema	2 (0.4)	16 (1.7)
Injection site rash	0	13 (1.4)
Injection site pruritus	8 (1.7)	12 (1.3)
Injection site hypersensitivity	0	7 (0.8)

Injection site hemorrhage	3 (0.6)	6 (0.7)
Injection site irritation	0	3 (0.3)
Skin and subcutaneous tissue disorders		
Any event	2 (0.4)	13 (1.4)
Erythema	2 (0.4)	5 (0.5)
Vascular disorders		
Any event	0	3 (0.3)
Hematoma	0	3 (0.3)

Source Data: Table SP3-31.1.2. Density per 100 person-years = 100 \* (number of AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the treatment period being summarized

*The applicant was asked to provide narratives for events of injection site hypersensitivity. The applicant clarified that In the Phase III integrated safety data, 9 albiglutide subjects (0.4%) and 3 all comparator subjects (0.1%) had preferred term events of injection site hypersensitivity. In the albiglutide arm two subjects withdrew from study drug, and 4 subjects had single events while 5 subjects experienced multiple events. The majority of events (7/9) resolved within 7 days and did not suggest a systemic hypersensitivity reaction. Two subjects were antibody positive and experienced > 20 injection site reactions each.*

#### Albiglutide vs. All comparators

A higher proportion of subjects in the albiglutide treatment group experienced an injection site reaction compared with all comparators (15.4% vs. 6.7%). A small number of subjects in the albiglutide group experienced a severe reaction (1.8 vs. 0 %), and there were no SAEs in either treatment group. Among the subjects who had ISRs, most only had 1 or 2 events.

A higher proportion of subjects in the albiglutide group experienced ≥11 events (11.7% vs. 3.9%), and a few subjects reported >20 events each compared with all comparators (5.5% vs. 2.6%, respectively). The applicant reviewed demographic data for 38 subjects who reported 1106 of the 1745 ISRs. The majority were women (30/38 subjects). Six subjects with >50 events each were all female, of non-Hispanic White race, and their ages ranged from 51 to 63 years.

***Reviewer Comment: The applicant was asked to provide additional information regarding subjects experiencing multiple (> 11) ISRs. The sponsor notes that the maximum intensity of ISRs per subject was most often mild. The most common reaction symptoms for the albiglutide-treated subjects in the ≥11 ISR subgroup were “erythema”, “pruritus” and “raised”. The median time to reaction was not markedly different across the subgroups and treatment arms (0-1 day). There was a trend for a higher proportion of female subjects among the albiglutide-treated arms. The proportion of subjects withdrawn due to an event was similar between the ≥11 ISR subgroup and the 1-10 ISR subgroup (15.8% to 13.6%). Medical***

**history in the area of immune system disorders (including allergies) was higher in the  $\geq 11$  ISR (47.4%, 18/38) subgroup compared to subjects experiencing 1-10 ISRS.**

Ten of the 38 subjects were anti-albiglutide antibody positive and discussed further below under antibody status.

Albiglutide vs. Active Injectable Comparators (Liraglutide, Insulin Lispro and Insulin Glargine)

Table 63 presents a summary of the characteristics of on-therapy injection-site reactions in the 3 active comparator open label studies conducted with injectables (liraglutide, lispro and insulin glargine). Overall injection site events were higher in the albiglutide group: albiglutide vs. liraglutide (12.9. vs. 5.4%); albiglutide vs. insulin lispro (9.5 vs. 5.3 %); albiglutide vs. insulin glargine (16.7 vs. 10%). There were more withdrawals in the albiglutide group when compared to the 3 other injectables. Most events were mild/moderate in intensity and the mean onset time of an ISR relative to the first dose was later in the albiglutide groups (ranged from 127.7 to 360.1 days) compared with the active comparator groups (ranged from 39.4 to 213.7 days).

**Table 63: GLP114179, GLP108486, and GLP112754 (Safety Population) Characteristics of On-therapy Injection Site Reactions**

	Study GLP114179		Study GLP108486		Study GLP112754	
	Albiglutide (N=404)	Liraglutide (N=408)	Albiglutide (N=285)	Pre-prandial Lispro Insulin (N=281)	Albiglutide (N=504)	Insulin glargine (N=241)
No. subjects with reactions,	52 (12.9)	22 (5.4)	27 (9.5)	15 (5.3)	84 (16.7)	24 (10.0)
No. subjects withdrawn due to reaction, n (%)	11 (2.7)	1 (0.2)	3 (1.1)	0	13 (2.6)	0
No. subjects who received treatment for reaction <sup>1</sup> , n (%)	16 (4.0)	5 (1.2)	8 (2.8)	0	18 (3.6)	0
No. events	188	37	135	22	488	57
<b>Intensity of event, n (%)</b>						
n	188	37	135	22	488	57
Mild	160 (85.1)	33 (89.2)	113 (83.7)	21 (95.5)	441 (90.4)	47 (82.5)
Moderate	28 (14.9)	4 (10.8)	22 (16.3)	1 (4.5)	42 (8.6)	10 (17.5)
Severe	0	0	0	0	5 (1.0)	0
<b>Duration (days)<sup>2</sup></b>						
n	187	37	132	22	485	57
Mean (SD)	26.3 (38.53)	21.4 (39.08)	17.7 (19.15)	31.4 (60.37)	13.1 (27.46)	19.3 (47.40)

Onset time (days) relative to first dose						
n	188	37	135	22	488	57
Mean (SD)	127.7 (61.38)	39.4 (49.22)	176.4 (102.32)	103.3 (101.36)	360.1 (246.43)	213.7 (214.73)
Number of events per subject, n (%)						
N	52	22	27	15	84	24
1 event	27 (51.9)	13 (59.1)	10 (37.0)	11 (73.3)	34 (40.5)	11 (45.8)
2 events	11 (21.2)	7 (31.8)	5 (18.5)	2 (13.3)	18 (21.4)	4 (16.7)
3 to 10 events	8 (15.4)	2 (9.1)	9 (33.3)	2 (13.3)	26 (31.0)	9 (37.5)
11 to 20 events	5 (9.6)	0	2 (7.4)	0	1 (1.2)	0
>20 events	1 (1.9)	0	1 (3.7)	0	5 (6.0)	0
Maximum intensity per subject <sup>3</sup>						
N	52	22	27	15	84	24
Mild	39 (75.0)	19 (86.4)	24 (88.9)	14 (93.3)	63 (75.0)	20 (83.3)
Moderate	13 (25.0)	3 (13.6)	3 (11.1)	1 (6.7)	18 (21.4)	4 (16.7)
Severe	0	0	0	0	3 (3.6)	0
Number of subjects with reaction symptoms <sup>4</sup>						
Redness /erythema	43 (82.7)	10 (45.5)	21 (77.8)	4 (26.7)	60 (71.4)	4 (17.4)
Itching/pruritus	30 (57.7)	5 (22.7)	15 (55.6)	1 (6.7)	52 (61.9)	0
Raised	10 (19.2)	1 (4.5)	14 (51.9)	0	24 (28.6)	2 (8.7)
Warmth	9 (17.3)	0	6 (22.2)	0	15 (17.9)	1 (4.3)
Other symptoms	9 (17.3)	14 (63.6)	10 (37.0)	12 (80.0)	28 (33.3)	20 (87.0)

Source: Modified from ISS Table 180 Page 556

Note: This summary presents on-therapy adverse events flagged by the investigator as injection site reactions.

1. Subjects with non missing information on treatment received for reaction.
2. Duration could not be calculated for the events that were ongoing or unresolved as the stop date was not available.
3. Only the event with the highest intensity was counted if a subject reported multiple episodes of events.
4. Subjects with non missing information for reaction symptoms.

### **Injection Site Reactions by Anti-Albiglutide Antibody Status**

Although most subjects who had ISRs were anti-albiglutide antibody negative, subjects who were antibody positive were more likely to have ISRs. The proportion of subjects who were anti-albiglutide antibody positive and experienced an ISR was 40.5% (47 of 116 subjects) compared with 14.2% (274 of 1927 subjects) who were antibody negative and experienced an ISR. While a number of subjects experienced many ISRs regardless of antibody status, the proportion of subjects with more than 20 ISRs was greater in anti-albiglutide antibody positive subjects (12.8% vs. 4.4%). ISR discontinuations in antibody positive subjects occurred in 5/45 subjects.

**Table 64: Summary Characteristics of Injection Site Reactions by Post dose Anti-Albiglutide Antibody Status**

	Anti-Albiglutide Antibody Positive	Anti-Albiglutide Antibody Negative
	(N=116)	(N=1927)
<b>Number of subjects with reaction</b>	47 (40.5)	274 (14.2)
<b>Number of events</b>	452	1286
<b>Number of events per subject<sup>1</sup></b>		
1 event	12 (25.5)	132 (48.2)
2 events	12 (25.5)	45 (16.4)
3 – 10 events	18 (27.7)	69 (25.2)
10 – 20 events	4 (8.5)	16 (5.8)
>20 events	6 (12.8)	12 (4.4)
<b>Maximum intensity of events per</b>		
Mild	31 (66.0)	209 (76.2)
Moderate	16 (34.0)	59 (21.5)
Severe	0	6 (2.2)
<b>Median onset (days) of event</b>		
Relative to first dose	190	274
Relative to preceding dose	0	1.0
<b>Median duration (days) of event<sup>3</sup></b>	6.0	7.0
<b>Action taken</b>		
Investigational product withdrawn	5 (1.1)	40 (2.1)
Subject received treatment for reaction	14 (12.1)	82 (4.3)

Source Data: Table 193 ISS page 585

1. Percentages are based on the number of subjects with injection site reactions
2. Only the event with the highest intensity was counted if the subject reported multiple episodes of events
3. Duration could be calculated for ongoing or unresolved events as of the data cut-off date

Antibody status in subjects experiencing > 11 ISR events:

Ten of the 38 subjects were anti-albiglutide antibody positive. The applicant states there were no severe ISRs for these 10 antibody-positive subjects, and onset of ISRs coincided with antibody appearance in 4/10 subjects. There was no association between antibody titer and proportion of reported ISR events, duration, or severity in these subjects. The sponsor notes that antibodies were not measured as frequently as ISRs occurred making it difficult to determine a temporal relationship between antibody status and ISRs. Of the 10 subjects with a positive antibody test, half had all mild ISRs and half had both mild and moderate ISRs.

**Reviewer Comment: Determination of an association between antibody status and multiple ISRs is limited by the small sample size, thereby precluding an understanding of the predictive value of antibody status and occurrence of an ISR. However a better understanding of this relationship may be derived from future trials designed to capture antibody levels at the time of event development.**

4MSU INJECTION SITE REACTIONS

Investigator-reported ISRs occurred for 16 subjects (1.1%) in the albiglutide treatment group (35 events) and 6 subjects (0.4%) in the all comparator treatment group (8 events). Most events were mild in intensity, and there were no severe or serious events. All events in the albiglutide treatment group occurred in anti-albiglutide antibody negative subjects. While most reactions resolved by day 7 there were a few that had a longer duration and are described below.

Subject 3441756986 had 3 events of 'excoriation injection site' and 3 events of 'scarred injection site' that took between 57 and 75 days to resolve.

Subject 3698757988 had 1 event of ISR that took 31 days to resolve.

One subject in the albiglutide group withdrew from treatment:

Subject 7763753988: 65 year old woman had a mild injection site reaction on study day 721. Study drug was subsequently withdrawn.

#### CUMULATIVE INJECTION SITE REACTIONS

ISRs occurred for 334 subjects (15.8%) in the albiglutide treatment group with 1780 events and 157 subjects (6.9%) in the all comparators treatment group with 455 events.

***Reviewer Comment: Cumulative data includes results from all active comparators. A more appropriate comparison is vs. placebo to eliminate confounding from active injectable comparators.***

#### RENAL STUDY (GLP114130) INJECTION SITE REACTIONS

There was a higher number of ISRs in the albiglutide group compared to sitagliptin treated subjects (8%, 20/249 vs. 3.7, 9/246%). There were no withdrawals due to ISRs and most events were mild. In the albiglutide group the proportion of subjects reporting events of ISR was higher for subjects with severe renal impairment (n=3, 15.8%) compared with mild (n=11, 8.6%) or moderate (n=6, 5.9%) renal impairment.

***Reviewer Comment: Conclusions regarding ISR development and renal impairment severity are limited by the small sample size.***

#### SYSTEMIC ALLERGIC REACTIONS (SARs)

Overall SARs identified by Standard MedDRA Query were balanced for the albiglutide vs. placebo group (1.8 vs. 1.9%, respectively) as well as albiglutide vs. all comparators (1.5 vs. 1.2%). The highest proportion of events occurred in the skin and subcutaneous disorders SOC for both treatment comparison groupings and were balanced between

treatment arms. A slight imbalance not in favor of study drug was noted in investigator identified SARs which was driven by a higher number of events in ISRs in the albiglutide arm (0.4% 8/2116 vs. 0).

Subjects receiving albiglutide experienced systemic allergic reactions of rash, angioedema and anaphylaxis. Hypersensitivity reactions of rash and urticaria have been observed in subjects taking albiglutide. While many of these events were not life threatening they are potential adverse reactions that should be included as warnings in the product label. In addition angioedema has also been reported with other GLP-1 receptor agonists. While many cases of angioedema in the albiglutide program were confounded with concomitant use of ACE inhibitors the relationship between the event and study drug could not be ruled out with complete certainty. Albiglutide should be used with caution in patients with a history of angioedema or with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema.

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

Two mechanisms were employed to review potential SARs: investigators flagged AEs they considered to be SARs (note- protocols did not have criterion provided for this determination) and a narrow standard MedRA query for anaphylaxis, angioedema, and severe cutaneous reactions was used to search for any additional events.

For each subject, the time to first occurrence of an SMQ-identified systemic allergic reaction was calculated as the number of days between the first dose date and the date of onset of the first on-therapy systemic allergic reaction plus 1 day. For subjects who did not report any systemic allergic reaction events, the time to an SAR was censored at days between the first dose and the date of the last dose plus 57 days.

### Albiglutide vs. Placebo

As depicted in Table 65, overall SARs in the albiglutide vs. placebo group were balanced (1.8 vs. 1.9%). A higher proportion of single events under the SOC of eye disorders were noted in the albiglutide group due to single events of **eye edema, swelling** and **eyelid edema**. Narrative review for these events did not suggest a trend for a safety signal although there was an overall paucity of information in the narrative reports. A higher proportion subjects in the placebo arm experienced event terms for angioedema.

**Table 65: On-therapy Systemic Allergic Reactions Identified by Standard MedDRA Query - Albiglutide vs. Placebo (P3-ISP)**

System Organ Class Preferred Term	Placebo (N=468)		Albiglutide (N=923)	
	n (%)	Number of	n (%)	Number of
Any event	9 (1.9)	13 / 1.55	17 (1.8)	18 / 1.00
<b>Skin and subcutaneous tissue disorders</b>				
Any event	8 (1.7)	10 / 1.19	13 (1.4)	14 / 0.78
Urticaria	5 (1.1)	7/0.83	9 (1.0)	9/0.50
Swelling face	0	0	2 (0.2)	2 / 0.11
Angioedema	3 (0.6)	3 / 0.36	1 (0.1)	1 / 0.06
Exfoliative rash	0	0	1 (0.1)	1 / 0.06
Idiopathic urticaria	0	0	1 (0.1)	1 / 0.06
<b>Eye disorders</b>				
Any event	0	0	3 (0.3)	3 / 0.17
Eye edema	0	0	1 (0.1)	1 / 0.06
Eye swelling	0	0	1 (0.1)	1 / 0.06
Eyelid edema	0	0	1 (0.1)	1 / 0.06
<b>General disorders and administration site conditions</b>				
Any event	0	0	1 (0.1)	1 / 0.06
Face edema	0	0	1 (0.1)	1 / 0.06

Source Data: ISS Table 173 Page 526

AE = adverse event; MedDRA = Medical Dictionary of Regulatory Activities.

Note: On-therapy events are those that have a start date on or after the first day of study medication and within 56 days after the end of study medication. On-therapy AEs that are identified as systemic allergic reactions based on a narrow standard MedDRA query list of preferred terms are presented in this summary. For each level of summarization, a subject was counted once if the subject reported 1 or more events. Percentages are based on the number of subjects in each treatment grouping. The system organ class (SOC) and preferred term within the SOC are presented by decreasing frequency of incidence for the albiglutide treatment grouping.

- Number of AEs = the total number of AEs at each level of summarization.  
Density per 100 person-years =  $100 * (\text{number of AEs} / \text{person-years})$ , where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the treatment period being summarized.

### Albiglutide vs. All Comparators

Table 66 lists on-therapy SARs identified by the MedDRA Query comparing albiglutide vs. all comparators. The proportion of subjects with any SAR event was comparable between groups (1.5% vs. 1.2%), with urticaria being the most common event in both groups. In the albiglutide group investigator identified SARs when not captured by the SMQ were generally cutaneous events (Table 67). SARs with preferred term events of angioedema and urticaria were balanced

**Table 66: On-therapy Systemic Allergic Reactions Identified by Standard MedDRA Query with at least 1 event in the albiglutide group with higher number compared to all comparators - Albiglutide vs. All Comparators (P3-ISP)**

System Organ Class Preferred Term	All Comparators (N=2116)		Albiglutide (N=2116)	
	n (%)	Number of AEs /	n (%)	Number of AEs /
Any event	27 (1.2)	32 (1.5)	32 (1.5)	39 / 1.16
<b>Skin and subcutaneous tissue disorders</b>				
Any event	24 (1.1)	24 (1.1)	24 (1.1)	29 / 0.86
Urticaria	17 (0.7)	16 (0.8)	16 (0.8)	20 / 0.59
Angioedema	5 (0.2)	3 (0.1)	3 (0.1)	3 / 0.09
Swelling face	3 (0.1)	3 (0.1)	3 (0.1)	3 / 0.09
Exfoliative rash	0	2 (0.1)	2 (0.1)	2 / 0.06
Idiopathic urticaria	0	1 (0.0)	1 (0.0)	1 / 0.03
<b>Eye disorders</b>				
Any event	0	4 (0.2)	4 (0.2)	4 / 0.12
Eye edema	0	1 (0.0)	1 (0.0)	1 / 0.03
Eye swelling	0	1 (0.0)	1 (0.0)	1 / 0.03
Eyelid edema	0	1 (0.0)	1 (0.0)	1 / 0.03
Periorbital edema	0	1 (0.0)	1 (0.0)	1 / 0.03
<b>Gastrointestinal disorders</b>				
Any event	1 (0.0)	4 (0.2)	4 (0.2)	4 / 0.12
Palatal edema	0	2 (0.1)	2 (0.1)	2 / 0.06
Lip swelling	0	1 (0.0)	1 (0.0)	1 / 0.03
Swollen tongue	1 (0.0)	1 (0.0)	1 (0.0)	1 / 0.03
<b>General disorders and administration site conditions</b>				
Any event	0	1 (0.0)	1 (0.0)	1 / 0.03
Face edema	0	1 (0.0)	1 (0.0)	1 / 0.03
<b>Immune system disorders</b>				
Any event	1 (0.0)	1 (0.0)	1 (0.0)	1 / 0.03
Anaphylactic reaction	0	0	1 (0.0)	1 / 0.03
<b>Respiratory, thoracic, and mediastinal disorders</b>				
Any event	2 (0.1)	1 (0.0)	1 (0.0)	0
Laryngeal edema	1 (0.0)	1 (0.0)	1 (0.0)	0

Source Data: ISS Table 172 Page 524

AE = adverse event; MedDRA = Medical Dictionary of Regulatory Activities. 1 Number of AEs = the total number of AEs at each level of summarization. Density per 100 person-years = 100 \* (number of AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the treatment period being summarized.

**Table 67: On-therapy Investigator-Identified Systemic Allergic Reactions - Albiglutide vs. All Comparators (P3-ISP)**

System Organ Class Preferred Term	All Comparators		Albiglutide (N=2116)	
	n (%)	Number of AEs /	n (%)	Number of AEs /
Any event	19 (0.8)	23 / 0.63	30 (1.4)	38 / 1.13
<b>Skin and subcutaneous tissue disorders</b>				

Any event	12 (0.5)	15 / 0.41	13 (0.6)	16 / 0.47
Angioedema	1 (0.0)	1 / 0.03	2 (0.1)	2 / 0.06
Pruritus generalized	1 (0.0)	1 / 0.03	2 (0.1)	5 / 0.15
Rash	0	0	2 (0.1)	2 / 0.06
Urticaria	6 (0.3)	7 / 0.19	2 (0.1)	2 / 0.06
Alopecia	0	0	1 (0.0)	1 / 0.03
Dermatitis allergic	3 (0.1)	4 / 0.11	1 (0.0)	1 / 0.03
Panniculitis	0	0	1 (0.0)	1 / 0.03
Rash generalized	1 (0.0)	1 / 0.03	1 (0.0)	1 / 0.03
Rash macular	0	0	1 (0.0)	1 / 0.03
<b>General disorders and administration site conditions</b>				
Any event	0	0	8 (0.4)	11 / 0.33
Injection site reaction	0	0	5 (0.2)	8 / 0.24
Injection site erythema	0	0	2 (0.1)	2 / 0.06
Injection site pruritus	0	0	1 (0.0)	1 / 0.03
<b>Gastrointestinal disorders</b>				
Any event	1 (0.0)	1 / 0.03	3 (0.1)	3 / 0.09
Diarrhea	0	0	1 (0.0)	1 / 0.03
Nausea	0	0	1 (0.0)	1 / 0.03
Vomiting projectile	0	0	1 (0.0)	1 / 0.03
Dry mouth	1 (0.0)	1 / 0.03	0	0
<b>Immune system disorders</b>				
Any event	4 (0.2)	4 / 0.11	2 (0.1)	2 / 0.06
Hypersensitivity	2 (0.1)	2 / 0.06	2 (0.1)	2 / 0.06
<b>Infections and infestations</b>				
Any event	0	0	2 (0.1)	2 / 0.06
Influenza	0	0	1 (0.0)	1 / 0.03
Skin infection	0	0	1 (0.0)	1 / 0.03
<b>Vascular disorders</b>				
Any event	0	0	2 (0.1)	2 / 0.06
Flushing	0	0	2 (0.1)	2 / 0.06
<b>Eye disorders</b>				
Any event	1 (0.0)	1 / 0.03	1 (0.0)	1 / 0.03
Eyelid edema	0	0	1 (0.0)	1 / 0.03
<b>Respiratory, thoracic, and mediastinal disorders</b>				
Any event	1 (0.0)	1 / 0.03	1 (0.0)	1 / 0.03
Oropharyngeal discomfort	0	0	1 (0.0)	1 / 0.03

ISS Table 174 Page 504.

### Narrative for SAR events in the albiglutide treatment group

Narrative review for 2 subjects experiencing adverse events of **exfoliative rash** in the albiglutide arm did not suggest a systemic process. These single events occurred on study day 229 and 629, respectively. Both cases of rash were localized to the left foot and resolved without treatment. In both cases action was not taken with study medication.

Subject 3696754986: 57 year old female experienced face and **lip swelling** 915 days after the first dose of study drug. The subject was not on an ACE inhibitor and additional clinical data was not provided. No action was taken with the study medication and the event resolved without treatment. Review of non-serious adverse events revealed that one month prior the subject developed folliculitis (treated with Bactrim) and developed a drug eruption described as a generalized rash which was felt to be due to Bactrim.

***Reviewer Comment: A follow up information request confirmed the development of a drug rash after starting Bactrim (verbatim: generalized rash to Bactrim reaction). Bactrim treatment was discontinued and the events of lip and face swelling and drug eruption resolved. The subject tested negative for anti-albiglutide antibodies throughout the study.***

Descriptions of 2 preferred term events of **palatal edema**

Subject 5701179009: 51 year old man with hypertension and hyperlipidemia developed **uvula edema** on study day 101. The subject was taking ramitens for hypertension and simvacor for hyperlipidemia. Additional details regarding the event were not provided in the narrative. No action was taken with the study medication and there was no treatment reported. The event was considered resolved on the same day.

Subject 1257486005: 65 year old male with a history of hypertension (treated with lisinopril) and dyslipidemia (treated with niacin and simvastatin) experienced a myocardial infarction on study day 142 requiring cardiac catheterization with stent placement. On study day 144 the subject complained of difficulty swallowing and was noted to have petechiae and **edema to the uvula** without stridor. Ear Nose and Throat consultation noted uvula edema from an allergic reaction to lisinopril. Treatment included dexamethasone and discontinuation of lisinopril resulting in improvement in symptoms. No action was taken with the study medication due to the event.

***Reviewer Comment: The etiology of uvula edema development is difficult to interpret with background lisinopril use and the temporal relationship to cardiac catheterization and stent placement.***

Narratives for cases of Angioedema

Three subjects in the albiglutide arm had single events of angioedema and are described below.

Subject 1001486015: 65-year-old female with a medical history of hyperlipidemia and hypertension (treated with lisinopril 10 mg daily), experienced swelling **of the lips and tongue** and renal insufficiency on study day 59. The subject was taking lisinopril for 9

months prior to participating in the study and lisinopril was discontinued and replaced with amlodipine after development of angioedema. Methylprednisolone was given to treat the angioedema, which resolved 5 days later. The subject's albiglutide dose was increased to 50 mg weekly 36 days after the serious adverse event of angioedema. Approximately 362 days after the first dose of albiglutide the subject experienced severe tracheobronchitis which was considered serious. No action was taken with the study drug due to either event. The subject tested negative for anti-albiglutide antibody.

***Reviewer Comment: Although a relationship to study drug cannot be excluded, the case is confounded by the presence of lisinopril which is associated with angioedema. In addition the subject responded to discontinuation of the ACEI and did not have a recurrence of symptoms despite up-titration to a higher albiglutide dose.***

Subject 3501754987: 59-year old male experienced **tongue swelling** and **angioedema** 717 days after the first dose of albiglutide requiring treatment with IV steroids. The subject had a history of hypertension and was on lisinopril at the time of the event. The ACEI was discontinued and the subject was started on losartan. He tested negative for antibodies to albiglutide. No action was taken with the study medication due to the event.

***Reviewer Comment: Follow up information revealed that the subject had started lisinopril 5 months prior to the event. Additional allergic type reactions were not reported after stopping lisinopril. The development of angioedema in this case appears to be related to the lisinopril.***

Subject 3699757986: 55-year old male experienced mild urticaria and mild lip angioedema 413 days after the first dose of investigational product. The subject was on enalapril for hypertension at the time of the event. The subject tested positive for the antibody to albiglutide at week 12. No action was taken with the study medication due to the events. The subject received diphenhydramine as treatment and the events were considered resolved. Narrative review also suggests that the subject was treated with azithromycin for an upper respiratory infection a few days prior to the events.

***Reviewer Comment: The administration of azithromycin a few days prior to development of mild urticaria and angioedema confound a determination of study drug causality in this case.***

#### Narratives for cases of Anaphylaxis

Subject 3432754986: 69 year old female experienced swelling of the tongue and shortness of breath categorized as an **anaphylactic reaction** on study day 733 days. The subject tested negative for the antibody to albiglutide. Lisinopril 20 mg was started 6 months prior to the anaphylactic reaction, and the dose was increased 2 months prior

to the event. The lisinopril was discontinued and no action was taken with the study medication.

**Reviewer Comment: Follow up information from the applicant revealed that the subject remained on albiglutide after discontinuation of the ACEI and completed 3 years of albiglutide treatment as per protocol. Per the applicant there were no other AEs in the final 3-year study database reported for this subject that was flagged as a potential SAR by either the investigator or the MedDRA SMQ search query for anaphylactic reaction, angioedema, and severe cutaneous adverse reactions.**

The following case was coded as Hypersensitivity but may represent a systemic allergic reaction of anaphylaxis.

Subject 1001179014: 50-year old female had a past medical history of hypertension (treated with triamterene/HCTZ from 2001), hypothyroidism (on levothyroxine from 2001), and diabetes (on metformin since 2002 and glimepiride since February 2010). The subject received the first dose of study drug in September of 2010. The subject began developing “dry skin” with itching late in 2010. In December 2010 she developed diffuse erythema on her arms, legs, and trunk for which study medication was held. Two months later by 23 Feb 2011, the rash resolved and study medication was resumed. The subject did well after the first two resumed doses. On 16 Mar 2011, she experienced an allergic reaction several hours after study drug administration described as a “generalized rash of the arms-legs-chest and back” with erythema and severe pruritus treated with methylprednisolone dose pack. Per the narrative the subject felt shortness of breath and did not seek medical care.

**Reviewer Comment: This adverse event was categorized as a systemic allergic reaction. However based on review of the narrative it appears the subject may have experienced a possible anaphylactic reaction. This is supported by the development of a diffuse rash within 90 days of starting investigational product. In addition the subject experienced a resolution of symptoms with study drug withdrawal and a recurrence of rash with shortness of breath upon rechallenge with albiglutide.**

#### Cases of study drug withdrawal

There were 8 withdrawals in the albiglutide group due to potential system allergic reactions. Withdrawal narratives for 7 cases are described below. Subject 1001179014 is described above.

Subject 3550753986: 63-year old male experienced mild flushing on the same day of the first dose of investigational product. On study day 21 the subject experienced severe projectile vomiting resulting in study drug discontinuation.

***Reviewer Comment: Due to the temporal relationship between the event of flushing and study drug administration a causal relationship cannot be ruled out. Of note, the subject did not have recurrent events of flushing.***

Subject 3517755986: 62-year old female experienced a severe **injection site reaction** described as redness, itching, swelling, warmth and hives requiring treatment with diphenhydramine on study day 162. The subject tested negative for the antibody to albiglutide. The investigator considered the event to be a systemic allergic reaction and the study medication was withdrawn.

Subject 5604486012: 61 year old women experienced a mild **injection site reaction** on study day 106.

Subject 8201486001: 54-year old female, 27 days after the first dose of albiglutide the subject experienced **moderate dermatitis allergic** considered non serious.

Subject 5701179012: 43-year old female developed mild **panniculitis** 3 days after the 22nd dose of albiglutide.

1296179006: 47-year old female experienced **generalized itching** 4 days after the first dose, 6 days after the second dose, 2 days after the third dose and 6 days after the fifteenth dose.

3464755987: 37-year old man experienced **generalized rash** of mild intensity on study day 278.

#### SARs in Antibody positive subjects

There were 4 albiglutide subjects who were antibody positive and experienced a potential SAR.

Subject 3603754982: 50-year old experienced mild flushing and mild oropharyngeal discomfort that occurred 15 minutes after the administration of albiglutide on study day 140. No action was taken with albiglutide due to the event. There was no treatment reported. The subject tested negative for antibody to albiglutide. There were no new medications and the subject was not on an ACEI.

***Reviewer Comment: Due to the temporal relationship between study drug administration and events of flushing and oropharyngeal discomfort a causal relationship cannot be ruled out.***

Subject 3672754982: 55 year old male experienced urticaria on study day 20 and 164. The subject tested positive for the antibody to albiglutide on at week 104 with an end point titer of 133. No action was taken with the study medication.

Subject 3467755986: 59-year old female experienced a mild rash on day 420 day. No action was taken with the study medication.

Subject 5602486032 57-year old male experienced mild injection site reactions on study day 112 and 188.

Subject 7072754999: 55 year old female developed urticaria on study day 191 (16 days after dose up-titration). There were no new medications at the time of the event.

**Reviewer Comment: The event of urticaria may have been caused by dose up-titration to the higher dose.**

**Reviewer Comment: There did not appear to be an overall pattern of temporal association between potential SARs and development of ant-albiglutide antibodies.**

#### 4MSU SYSTEMIC ALLERGIC REACTIONS

During the safety update period on-therapy investigator-reported potential SARs occurred for 6 subjects (0.4%) in the albiglutide treatment group (11 events) and 5 subjects (0.3%) in the all comparator treatment group (6 events). The SMQ search identified 4 subjects (0.3%) with 4 events in the albiglutide treatment group and 4 subjects (0.3%) with 4 events in the all comparator treatment group.

One subject in the albiglutide group with an event of anaphylaxis (subject 3432754986) described in the BLA submission above was change from a non-serious to serious event. There were no additional SAEs in the albiglutide group or study drug withdrawals during the 4MSU. One subject in the placebo group experienced angioedema leading to study drug discontinuation.

#### CUMULATIVE SYSTEMIC ALLERGIC REACTIONS

In the P3-ISP on-therapy investigator reported potential SARs occurred for 1.7%, (35/2116 subject) in the albiglutide treatment group and 1.0%, (22/2284 subjects) in the all comparator treatment group. SARs were most common in the skin and subcutaneous disorders SOC in both albiglutide and all comparators treatment groups (0.8% and 0.6 %, respectively), with many subjects in the albiglutide arm experiencing single cutaneous rash events. Three (0.1%) subjects in the albiglutide arm had events of generalized pruritus and urticaria and 2 subjects (0.1%) had events of angioedema and allergic dermatitis. The overall incidence of these events was balanced when

compared to all comparators except in the preferred term event of angioedema which occurred in higher proportion in the all comparator arm (0.3%, 7 subjects). A higher proportion of subjects treated with albiglutide had potential SARS related to injections site reaction (0.4% vs. 0).

The SMQ identified SARs occurred in 1.7% (35/2116 subjects) in the albiglutide and 1.3% (30/2284 subjects) in all comparators. Urticaria was the most common SMQ-identified potential SAR, and the proportions of subjects reporting the event were similar for both treatment groups (0.9% albiglutide vs. 0.8% all comparators). Angioedema occurred in a higher proportion of subjects in the all comparators groups (0.3% vs. 0.13%). One subject in the albiglutide group had a preferred term event of anaphylaxis.

***Reviewer Comment: The reviewer identified another potential anaphylactic event in the albiglutide arm that was not coded as anaphylaxis.***

#### RENAL STUDY (GLP114130) SYSTEMIC ALLERGIC REACTIONS

In the renal impairment study the incidence of SARs identified by the narrow SMQ query was 1.2% in the albiglutide treatment group (3 of 249 subjects, 3 events) and 0.8% in the sitagliptin treatment group (2 of 246 subjects, 2 events). Investigator-identified SARs were reported in 0.8% of subjects in each group.

Subject 1486130003: 59-year old male on a lisinopril for hypertension (unspecified start date) developed **angioedema** (mild lip swelling) on study day 162 that was treated with one dose of diphenhydramine. Study drug was continued without sequeale. The subject tested negative for the anti-albiglutide antibody

Subject 5619130001: 71-year old female developed mild **face edema** on study day 116. The subject was on enalapril which was discontinued due to the event. There was no other treatment reported and the event was considered resolved. The subject tested negative for the anti-albiglutide antibody

Subject 8001130050: 65- year old female developed mild **lip swelling** on study day 16 treated with cetirizine. The subject was not on an ACEI. No action was taken with the study medication due to the event and the subject was treated with cetirizine and the event was considered resolved. The subject tested negative for the anti-albiglutide antibody.

Subject 3309130011: 55-year old female with a history of hypertension (treated with an angiotensin receptor blocker -losartan) and a history of dyspepsia developed mild **allergic dermatitis of the neck** on study day 71. The study drug was continued and the subject received treatment with loratadine. On study day 306 she developed melena and hematemesis and was hospitalized. Endoscopy reveal gastric ulcers. No action

was taken with study medication. The subject tested negative for the anti-albiglutide antibody.

Subject 1448130009: 71-year old male on study day 19 developed mild **rash** of the right wrist which resolved with steroid cream. On study day 27 he developed a mild **rash** on his feet which resolved with steroid cream. The study drug was discontinued. The subject was taking the ACEI benazepril at the time of the events.

***Reviewer Comment: The temporal relationship to the initiation of study drug and events of rash (day 19 and 27) suggest a possible relationship to study drug.***

## PANCREATITIS

Overall there was an imbalance between serious events of pancreatitis in the albiglutide arm (3 events (0.2%) vs. 0 in placebo). The Pancreatitis Adjudication Committee adjudicated 47 cases of interest (23 AE/SAEs suspicious for pancreatitis and 24 abnormal lipase measurements  $\geq 3 \times$  ULN) across the 8 Phase III studies. Of these 47 cases “**definite or probable pancreatitis**” with at least a possible relationship to study treatment had been adjudicated in 6 of 2,365 subjects receiving albiglutide, 2 of 408 subjects receiving liraglutide (Study GLP114179), and 0 of 2122 subjects receiving other comparators. Across the 8 Phase III studies, the cumulative (through the 4MSU) incidence rate of pancreatitis for albiglutide was 1.4/1,000 person-years and 0.4 in all comparators and 7.1/1000 person years in liraglutide. In the program one subject treated with albiglutide had a fatal event necrotizing pancreatitis that was related to an ERCP procedure. The label should include the class risk of pancreatitis as described with other GLP-1 agonists in the warnings section. Pancreatitis should remain an event of special interest in all future studies. Enhanced pharmacovigilance for events pancreatitis and pancreatic cancer should be implemented.

In the Phase III program, pancreatitis was a safety event of special interest. Investigators were instructed to monitor subjects closely for symptomatology suggestive of pancreatitis (e.g., persistent and/or severe abdominal pain, nausea, and vomiting) and to report all suspected cases. Specific electronic case report form (eCRF) pages were designed to collect detailed clinically relevant information on any suspected cases of pancreatitis.

Subjects diagnosed with pancreatitis by appropriate laboratory studies and other diagnostic testing were to be withdrawn from randomized study medication and should not have been rechallenged with study medication.

In August 2009, shortly after the initiation of the Phase III program, the protocols for

5 core studies (GLP112753, GLP112754, GLP112755, GLP112756, and GLP112757) were amended to add amylase and lipase baseline measurements and exclusion criteria for lipase or elevated amylase isoenzyme levels suggestive of a pancreatic etiology. Baseline amylase and lipase levels were obtained from baseline samples collected for biomarker analysis (the sponsor notes that assessments were not available for all subjects enrolled prior to the protocol amendment). In all Phase III studies, except GLP114130, subjects were excluded from study participation if the lipase result was above the upper limit of normal (ULN) or if elevated amylase isoenzyme levels suggested a pancreatic etiology of isoenzyme elevation

- For 7 Phase III studies (excluding GLP114179), amylase and/or lipase levels measured after study drug administration were assessed as needed at the investigators discretion.
- In study GLP114179, amylase and lipase levels were measured for all subjects at Week -1, Week 12 and Week 32 (end of treatment).
- In study GLP114130, subjects with elevated screening/baseline lipase were eligible to participate if asymptomatic and free of a history of pancreatitis.
- In the Phase II study GLP114856, amylase and lipase were assessed at Week – 1 (as a baseline value) and Week 17 (end of treatment).

In the Phase III development program potential events of pancreatitis and pancreatic enzyme elevations were adjudicated by a blinded independent committee (PAC). The PAC also reviewed abnormal amylase and/or lipase values ( $\geq 3X$  ULN) regardless of the presence or absence of clinical signs or symptoms to determine if there was a suspected event of pancreatitis requiring formal adjudication. The PAC was comprised of 3 physicians with expertise in gastroenterology. All events were reviewed and adjudicated independently in a blinded fashion, and discussed at a full committee meeting. If a consensus decision was not made the chairman determined the final adjudication of the pancreatitis event.

Three primary mechanisms were utilized to identify adverse events of interest for PAC review and adjudication: 1) investigator-reported AEs of pancreatitis, 2) Standard MedDRA Queries with both narrow and broad SMQs for acute pancreatitis, 3) routine review of all reported SAEs

Abnormal amylase and/or lipase measurement ( $>3X$  ULN), independent of clinical evidence were assessed by the PAC.

The PAC adjudication included all phase 3 studies and studies (GLP114856, GLP108372, GLP110932, GHF112670).

Table 68 details probability criteria employed by the PAC in determining the probability of pancreatitis.

**Table 68 Criteria for Assessing the Probability of Pancreatitis**

Probability of Pancreatitis	Abdominal Pain	Lipase >3X ULN (or 300), and/or Amylase >5X ULN (or	Imaging: Positive CT or MRI or Ultrasound
Definite	+	+	+
Probable	+	-	+
	+	+	-
	-	+	+
Possible (Must meet laboratory or imaging or imaging criteria)	-	+	-
	-	-	+
Not Diagnostic	Not specific	No laboratory data or data do not satisfy	No laboratory data or data do not satisfy criteria
Not Likely	+/-	-	-

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The PAC also made an assessment of the relationship of study treatment to pancreatitis events classified as Definite, Probable, or Possible. The treatment relationship was classified as Definite, Probable, Possible, or Unlikely Alternate Etiology. A classification of Definite could only be made if there was a rechallenge of study treatment.

17 subjects reported AEs (17 SAEs and 3 nonserious AEs) that were adjudicated by the PAC. The sponsor notes that 1 additional subject had a screening phase SAE of pancreatitis prior to randomization and 1 subject in the albiglutide (7764753989) group was adjudicated after BLA data transfer and is described below.

Subject 7764753989: 68-year old male with a history of hypertension, dyslipidemia, and chronic renal insufficiency developed cholecystitis on study day 853. The PAC report states that the event was adjudicated as not likely pancreatitis noting that cholecystitis was evident on CT and resolved with gallbladder drainage.

***Reviewer Comment: The etiology of pancreatitis in this case is confounded by the presence of cholecystitis.***

17 subjects adjudicated by PAC for AEs: Of these 7 received albiglutide and 9 were in all comparators and 1 did not receive therapy (screen failure). Details for these adjudicated cases are delineated below.

- 10 subjects ( 6 albiglutide: 4 liraglutide) adjudicated as **definite, probable, or possible pancreatitis**
  - 6 albiglutide-treated subjects:
    - 2 **definite pancreatitis** adjudicated the relationship to study drug as unlikely/alternate etiology

- 4 **probable** pancreatitis; 3 adjudicated cases determined to be probably related to study treatment and 1 was determined to be possibly related to study treatment
- 4 Liraglutide – treated subjects:
  - 1 **probable** pancreatitis with possible relationship to study drug
  - 3 **possible** pancreatitis (1 definitely related, 1 probably related, and 1 possibly related)
- 5 subjects (2 albiglutide, 1 liraglutide, 1 glimepiride, and 1 placebo-treated subject) adjudicated as **not likely** pancreatitis
- 2 subjects (1 glimepiride: 1 insulin glargine): adjudicated as **not diagnostic** of pancreatitis

Brief description of the albiglutide treated subjects adjudicated as **definite or probable or possible** pancreatitis with a possible or probable relationship to study drug are described below.

Subject 3663753982: 44-year old female with a history of dyslipidemia (treated with statins), and hepatitis C developed acute pancreatitis on study day 561. The subject reported right upper quadrant pain, nausea, vomiting and a 20 pound weight loss over 1 to 2 months prior to admission. She did not have an alcohol history or family history of pancreatitis. Lipase was elevated to 797 U/L (normal range: 0 to 59 U/L) and a computed tomography scan of the abdomen revealed an unremarkable pancreas. The study medication was withdrawn and the event resolved. The event was adjudicated as **probable** pancreatitis and probably related to study treatment.

***Reviewer Comment: The narrative lacks data regarding the evaluation of other potential etiologies of pancreatitis such as hypertriglyceridemia or gallstones. The PAC report notes that the subject was in a Hepatitis C study and therefore the contribution of the Hepatitis C investigational medication is difficult to assess. Due to the overall paucity of data a relationship between albiglutide and pancreatitis in this subject is uncertain but cannot be rule out.***

Subject 3443754986: 63-year old male with a history of obesity, herpes simplex type 2, hyperlipidemia, and non-alcoholic fatty liver, experienced pancreatitis on study day 873 (lipase was 523 U/L; amylase, LFTs, and triglycerides were normal and remained normal). MRI revealed acute focal pancreatitis and sludge in the gallbladder and nuclear medicine hepatobiliary scan showed acute cholecystitis. The study medication was withdrawn and pancreatitis resolved. The event was adjudicated as **probable** pancreatitis with a possible relationship to study drug.

***Reviewer Comment: Although a relationship between albiglutide and pancreatitis cannot be excluded the presence of sludge in the gallbladder could be contributory and confounds determination of causality in this case.***

Subject 3551757987: 58-year-old male with dyslipidemia developed epigastric pain and pancreatitis on study day 554. At initial hospitalization serum lipase was elevated at 3946 U/dL (normal range: 23 to 300 U/dL) and an ultrasound of the right upper quadrant of the abdomen showed hepatomegaly, fatty infiltration of the liver and chronic pancreatitis. The event was adjudicated as **probable** pancreatitis with a possible relationship to study treatment.

Subject 3611757988: 61-year-old male with a history of dyslipidemia experienced pancreatitis on study day 151. Ultrasound of the gallbladder was unremarkable and CT of the abdomen and pelvis revealed no pancreatic abnormality. Presenting lipase was elevated to 1135 U/L (normal range: 23 to 203 U/L) and amylase was increased to 215 U/L (normal range: 30 to 110 U/L). The subject was treated for acute pancreatitis and discharged with pancreatitis resolution. The event was adjudicated as **probable** pancreatitis with a probable relationship to study treatment.

***Reviewer Comment: The development of pancreatitis 151 days after the start of study drug is suggestive of a possible relatedness of the event to drug product. However, the narrative does not provide information regarding underlying risk factors.***

Cases of **definite** pancreatitis adjudicated as unlikely related to study drug are briefly summarized below.

Subject 3781757980: 69 -year-old male presented to the emergency department complaining of abdominal pain, nausea with vomiting and fever. Computed tomography scan of the abdomen confirmed acute pancreatitis. Admission labs were notable for elevated lipase of 1968 U/L (reference range: 55 to 406 U/L) and white blood cells 6.2 gl/L (reference range: 3.8 to 10.8 gl/L). The subject was diagnosed with viral pancreatitis and study medication was withdrawn with resolution of pancreatitis. The case was adjudicated as **definite** pancreatitis with an unlikely alternate etiology. The PAC notes that it is unclear why the case was labeled viral.

***Reviewer Comment: The narrative does not provide sufficient information to support the diagnosis of viral acute pancreatitis. Serologies for viruses implicated in the development of pancreatitis were not provided (Mumps, coxsackievirus, hepatitis B, cytomegalovirus, varicella-zoster, herpes simplex, HIV). A relationship between study drug and the development of pancreatitis cannot be excluded as the subject recovered after withdrawal of study medication.***

Subject 1255130002: 73-year old male with a history of hypertension, dyslipidemia and chronic renal insufficiency was found 3 months after the start of study medication to have an incidental finding of 2 pancreatic cysts which were not evident on a previous CT performed 2 years prior. On study day 159 the subject was admitted to the hospital

with pancreatitis (lipase 4895 (73-393) after he underwent an endoscopic ultrasound and fine-needle aspiration of the pancreatic cyst. The same evening as the biopsy he developed abdominal pain. His course was complicated with a new 6cm pseudocyst, necrotizing pancreatitis, life-threatening septic shock and multi-organ failure resulting in death. The events pancreatitis, pancreatic pseudocyst and necrotizing pancreatitis were adjudicated by the PAC to be consistent with **definite** acute pancreatitis and unlikely attributable to investigational product.

**Reviewer Comment: This case of pancreatitis is likely due to the ERCP procedure.**

Subject 3755754982: 39-year-old male without significant past medical history presented to the emergency room with a five-day history of nausea, vomiting and left upper quadrant abdominal pain on study day 551. The subject left against medical advice. Social history included four beers the night before development of abdominal pain. Unscheduled lipase drawn 2 months later was 80 U/L (local laboratory draw and normal ranges not provided). Drug was continued throughout and subsequent to the event. The event was adjudicated as **not likely** pancreatitis.

## PANCREATIC ENZYMES

The sponsor considered data from study GLP114179 as the primary focus for pancreatic enzyme analyses, as it was the only Phase III study that assessed on-therapy amylase and lipase levels at scheduled time periods (screening, week 12 and week 32). By protocol, some subjects with an abnormal amylase could remain in the study if there was a normal lipase. All subjects with an abnormal lipase at baseline were to have been excluded. One subject with an abnormal lipase was maintained in the study (protocol violation).

Amylase or lipase values  $\geq 3 \times \text{ULN}$  were pre-defined as potentially clinically concerning. The PAC then adjudicated both the probability that the laboratory abnormality was indicative of acute pancreatitis and considered the potential relationship of this event to use of blinded investigational product.

- Mean lipase levels were similar at baseline and week 32 between albiglutide and liraglutide treated subjects.
  - Baseline lipase Mean U/L (SD): albiglutide 32.5 (14.33) and liraglutide 33.1 (12.38)
  - Week 32 lipase Mean U/L (SD): albiglutide 45.9 (51.53) vs. Liraglutide 49.1 (33.64)

- Week 12 lipase levels were higher in the liraglutide arm Mean U/L(SD): albiglutide 44.6 (34.94) vs. Liraglutide 55.3 (47.28).
- Mean amylase levels were similar at all time points.
- Increases in the numbers of individual subjects with abnormal lipase values were observed at Week 12 and Week 32, with more subjects with abnormal lipase values in the liraglutide group than in the albiglutide group at both time points.
- 12 subjects in each of the treatment arms (albiglutide and liraglutide) had abnormal lipase measurements  $\geq 3 \times \text{ULN}$ ; there were no amylase values  $\geq 3 \times \text{ULN}$
- In Study GLP114179, a total of 21 subjects reported 22 abnormal lipase laboratory results ( $\geq 3 \times \text{ULN}$ ) meeting the criteria for PAC adjudication (12 subjects in the albiglutide treatment group and 9 subjects in the liraglutide treatment group)

All 12 abnormal lipase measurements in the albiglutide group were adjudicated by the PAC. Among the 12 liraglutide-treated subjects with abnormal lipase measurements: 9 subjects had abnormal laboratory values only that required adjudication by the PAC (3 subjects with abnormal laboratory values and concurrent AEs had only the AEs adjudicated by the PAC as the AEs occurred before the abnormal lipase measurements).

- For two events (one in each treatment group) the PAC concluded that the laboratory abnormality in association with abdominal pain was consistent with **probable** pancreatitis.
- For 13 events (7 in the albiglutide treatment group (and 6 in the liraglutide treatment group), the PAC concluded that the temporal relationship supported a probable or definite relationship of the laboratory abnormality to investigational product (Table 69).

**Table 69: PAC adjudication results for albiglutide and liraglutide treated subjects with lipase values  $\geq 3 \times \text{ULN}$  (Study GLP114179)**

Study ID / Subject ID	Treatment Assignment	Probability of Pancreatitis/ Related to Study Drug	PAC Comments
GLP114179 / 1015179012	Albiglutide	Possible / Probable	Normal lipase while on placebo. Elevated lipase while patient on study medication.
GLP114179 / 1031179015	Albiglutide	Possible / Definite	Lipase was normal on placebo. Lipase increased during drug treatment & returned to normal after stopping study drug. Lipase increased again after restarting study drug.
GLP114179 / 1050179006	Albiglutide	Possible / Probable	Abnormal lipase and amylase recorded at end of treatment. Returned to normal off therapy.
GLP114179 / 1069179006	Albiglutide	Possible / Probable	Lipase and amylase elevated at end of study period. Returned to normal on repeat testing off drug.
GLP114179 / 1086179026	Albiglutide	Possible / Probable	Lipase increased on Day 87 of treatment and was again increased to 508 at the end of treatment. No repeat follow-up values are available
GLP114179 / 1113179003	Albiglutide	Possible / Possible	Rise in both amylase and lipase while on study drug. Persistent mild increase in lipase at the end of study.
GLP114179 / 1215179025	Albiglutide	Possible / Possible	Lipase normal initially during study. Increased on last blood draw . Amylase normal. No follow-up lab available.
GLP114179 / 1317179003	Albiglutide	<b>Probable / Probable</b>	Rise in lipase while on drug. Associated abdominal pain near the end of study. Study drug stopped. No other potential etiology.
GLP114179 / 1337179026	Albiglutide	Possible / Possible	Rise in amylase/lipase while on study drug. Persistent elevation of lipase during study drug period. Bloating/gas reported at end of treatment.
GLP114179 / 8305179024	Albiglutide	Possible / Probable	Lipase and amylase increased during study. Patient reported to have dyspepsia around the same time. ? drug was stopped and restarted with mild rise in lipase recorded. Lipase normal at end of study.
GLP114179 / 8700179001	Albiglutide	Possible / Possible	Labs increased transiently while on study medication. No interruption in study medication.
GLP114179 / 8708179005	Albiglutide	Possible / Possible	Lipase increased while patient was on study medication. Lipase decrease after completing study and was mildly abnormal on last determination.

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Study ID / Subject ID	Treatment Assignment	Probability of Pancreatitis/ Related to Study Drug	PAC Comments
GLP114179 / 1074179002	Liraglutide	Possible / Possible	Transient rise in amylase/lipase while of study medication. Since labs returned to normal while on drug the relationship is possible rather than probable.
GLP114179 / 1086179017	Liraglutide	Possible / Probable	Lipase elevated during and at the end of study period. Lipase decreased and only mildly elevated with repeat testing few days later.
GLP114179 / 1118179005	Liraglutide	Possible / Possible	Transient rise in lipase and amylase during treatment. Labs returned to normal despite continued study medication.
GLP114179 / 1160179020	Liraglutide	Possible / Definite	Lipase and amylase returned to normal after stopping study drug. Lipase increased again after restarting study medication.
GLP114179 / 1284179004	Liraglutide	Possible / Probable	Normal labs during placebo. Persistent (on repeated measures) rise in amylase and lipase while on study drug. No follow-up labs are available.
GLP114179 / 1293179002	Liraglutide	Possible / Possible	Transient rise in lipase while on study drug. Lipase returned to normal and stayed normal despite continuing study drug.
GLP114179 / 1390179004	Liraglutide	Possible / Definite	Elevated lipase while on study drug. Drug was interrupted and restarted after decrease in lipase. Lipase increased again when checked at the end of study (positive rechallenge).
GLP114179 / 1460179006	Liraglutide	Probable / Possible	Rise in lipase with abdominal pain suggestive of pancreatitis while on study drug.
GLP114179 / 8708179001 <sup>1</sup>	Liraglutide	Possible / Definite	Both amylase and lipase increased while on study drug. Lipase decreased after stopping study drug and amylase returned to normal. Lipase increased again after restarting study drug. Both amylase and lipase were mildly increased after stopping the drug again. Amylase later returned to normal.
	Liraglutide	Possible / Definite	

Source Data: Listing PAC-2, GLP114179 CSR, Listing 16.1.7-1.1.

1. This event was captured as an AE of elevated lipase with an onset date of 01Feb2011 and is reported in Table 8.

One additional subject 3509753980: 50 year old man had normal baseline lipase sample. He developed an elevated lipase level ((188 U/L) nml not provided) with associated abdominal discomfort. Additional details not provided. The case was adjudicated as **probable** pancreatitis with a possible relationship to study drug.

There was 1 subject in the albiglutide group (Subject 1250179020) who discontinued study treatment due to the AEs of lipase increased and blood amylase increased vs. 3 in the liraglutide arm.

Subject 1250179020: 64-year-old Asian male with a history of dyslipidemia experienced an increase in lipase 86 days after the first dose of study medication (75 U/L [normal range: 7-60 U/L]). On study day 133 he had an increase in blood amylase (113 U/L [normal range: 29-103 U/L]). Study treatment was discontinued because of these events. The investigator considered the events of lipase increased and blood amylase increased as related to study medication

In the Phase II study GLP114856 (clinical BE), amylase and lipase were assessed at Week -1 (as a baseline value) and Week 17 (End of Treatment). In this study, 3 subjects had abnormal lipase measurements ( $\geq 3X$  ULN) sent for review and adjudication by the PAC. The PAC adjudicated each of these 3 cases as possible pancreatitis.

The sponsor did not include these cases in the incidence rate calculations since the study did not include active- or placebo controls.

Brief descriptions are provided below.

Subject 1161856018: 74 year old female with a past medical history of hyperlipidemia on study day 120 (6 days after the last dose of study medication) she experienced increased amylase 160 (baseline 30, normal 29-103 U/L) and lipase 927 (baseline was 42; normal (7-60 I/L). No other symptoms or imaging provided. Labs returned to baseline one month later. The event was adjudicated as **possible** pancreatitis with a *probable* relationship to study drug.

The following cases were adjudicated as **possible** pancreatitis with *possible* relationship to study drug.

Subject 3520856991: the subject had normal lipase and amylase a week prior to starting study drug. On study day 120 (after study completion) lipase was 3x ULN (labs not provided) no additional information provided

Subject 3442856900: 56-year old male with a history of hypertension and dyslipidemia received one dose of study medication and withdrew (due to a new job). Approximately 51 days after the first dose of study drug he developed an elevation in amylase 124

(baseline 53, normal 29-103 U/L) and lipase 282 (baseline was 59; normal (7-60 U/L) which normalized a few weeks later.

#### 4MSU PANCREATITIS

Four subjects in the albiglutide treatment group (3 on-therapy events and 1 post-therapy event) compared to none in all comparators reported treatment-emergent AEs suspicious for pancreatitis. There were no post-baseline amylase or lipase measurements requiring adjudication ( $\geq 3 \times$  ULN) during this period.

#### CUMULATIVE PANCREATITIS

The PAC adjudicated 47 cases of interest (23 AE/SAEs suspicious for pancreatitis and 24 abnormal lipase measurements  $\geq 3 \times$  ULN) across the 8 Phase III studies. Of these 47 cases of interest, definite or probable pancreatitis with at least a possible relationship to study treatment had been adjudicated in 6 of 2,365 subjects receiving albiglutide, 2 of 408 subjects receiving liraglutide (Study GLP114179), and 0 of 2122 subjects receiving other comparators. Across the 8 Phase III studies, the incidence rate of pancreatitis for albiglutide has decreased from 1.6/1,000 person-years to 1.4/1,000 person-years.

Table 70 depicts incidence rates for cases adjudicated by the PAC as definite or probable pancreatitis with at least a possible relationship to study treatment in the Phase III program.

**Table 70: Adjudicated Cases of Definite or Probable Pancreatitis with At Least Possible Relationship to Study Treatment in the Phase III Program for Albiglutide**

Definite or Probable Pancreatitis With at Least Possible Relationship to Study Treatment (Adverse Events and Abnormal Lipase Values) Through the Common 120-Day Safety Update Report Cut-Off Date of 14 Dec 2012	Number of Subjects	Person-Years <sup>1</sup>	Incidence Rate per 1,000 Person-Years
Albiglutide	6	4235.3	1.4
All comparators	2	4557.8	0.4
Liraglutide	2	283.3	7.1
Other comparators	0	4274.5	0

Source Data: 120-day Table 17page 97.

1. Total Person-Years for the 8 Phase III Studies: includes the cumulative person-years through the common integrated Safety Update Report cut-off date of 14 Dec 2012 in the 5 ongoing studies plus the total person-years in the completed Phase III studies (GLP114179, GLP108486, and GLP114130). Total exposure (person-years) for liraglutide is from the liraglutide treatment group in GLP114179)

Narratives for cases adjudicated as **possible** pancreatitis with possible relationship at the time of the 4MSU

Subject 3789753986: 74-year-old female experienced abdominal pain and pancreatitis 1093 days after the first dose of albiglutide, and 15 days after the last dose. Amylase

was 179 U/L (normal upper limit: 125 U/L) and lipase was 363 U/L (normal upper limit: 51 U/L). Computed tomography of the abdomen was normal. The event was assessed by the investigator as not related to study treatment.

**Possible** pancreatitis with unlikely relationship to study drug:

Subject 3656754988: 67-year-old male experienced a serious event of acute pancreatitis 686 days after the first dose of albiglutide, and 375 days after the last dose. Lipase was 637 U/L (normal upper limit: 37 U/L) and a CT scan showed chronic pancreatitis.

Adjudicated as **not likely** pancreatitis:

Subject 7764753989: 67-year-old male experienced acute cholecystitis 853 days after the first dose of study medication, and 6 days after the last dose. Amylase was 137 U/L (normal upper limit: 100 U/L) and lipase was not reported. An abdominal ultrasound revealed a thick gallbladder wall (consistent with recent inflammation). The event was assessed by the investigator as not related to study medication

Subject 3773753989: 59-year-old female experienced an AE of pancreatitis 859 days after the first dose of albiglutide, and 4 days after the last dose. The subject had symptoms of epigastric pain with an amylase of 46 U/L (normal upper limit: 100 U/L), and lipase was not reported. The event was not resolved at the time of the data cut and was assessed by the investigator as not related to study treatment and the subject continued in the study.

## PANCREATIC TUMORS

### Albiglutide:

- Subject 3431756987 46-year-old white male on study day 200 was found to have benign neuroendocrine tumor (**carcinoid**) in the head of the pancreas.
- Subject 354675988 (originally identified in the 4MSU as 3546754003) 58 year old female was found on study day 1025 to have a benign pancreatic neoplasm. The applicant provided additional follow up information indicating that a 17 mm by 13 mm partially calcified cyst in the inferior margin of the head was identified during an abdominal CT scan conducted (b) (6) as a result of persistent abdominal discomfort; the cyst was not seen on prior CT dated (b) (6). An abdominal MRI confirmed the finding. Local laboratory values revealed an amylase of 128 U/L (no reference range provided), a lipase of 557 U/L, and a CA 19-9 (carbohydrate antigen 19-9) of 8 U/L (no reference range provided). Subsequently, an endoscopic ultrasound with biopsy was successfully performed. The aspirate from the biopsy showed an amylase value of 106,000 U/L and a CEA (carcinoembryonic antigen) value of 808 µg/L (reference range not provided); pathology results revealed **benign serous cystadenoma**

The following 2 cases of malignancy are described in greater detail under fatalities (Section 7.3.1).

- Subject 3403757986 reported a fatal **bile duct cancer** on day 996 , initially reported to be of possible pancreatic origin. Further work up led to the diagnosis of cholangiocarcinoma with the primary site of malignancy remaining unknown.
- Subject 3614756987 reported a fatal SAE of **metastatic pancreatic carcinoma** on study day 694.

Comparator:

Subject 3873757986 on pioglitazone was found to have pancreatic adenocarcinoma on study day 17.

***Reviewer Comment: The development of pancreatic cancer 17 days after starting pioglitazone does not support a causal relationship.***

## DIABETIC RETINOPATHY

Diabetic retinopathy was considered an adverse event of interest because it was expected that the long duration of the trials and the reduction in HbA1c would lead to an improvement in diabetic retinopathy. Overall a higher incidence of on-therapy retinopathy was observed in albiglutide treated subjects when compared to placebo (3.6 % vs. 1.7%, respectively). The majority of events were background retinopathy with a small percentage of subjects (<1%) developing proliferative retinopathy. Data regarding dose effects are confounded by small event numbers in the forced titration study and poorer glycemic control in subjects who up-titrated to the 50 mg dose in optional studies. In addition the applicant notes that funduscopy was not conducted in a rigorous manner therefore baseline retinopathy status may not have been accurately captured. Diabetic Retinopathy events should be monitored in the dedicated cardiovascular outcomes study as well as future studies as an adverse event of interest with standardized baseline retinopathy assessments and follow up implementation.

In the Phase III program, subjects with active proliferative retinopathy were excluded from participation. At screening, subjects underwent visual acuity tests using standard snellen eye examination and funduscopy (dilation was preferred, but not required), and their diabetic history was taken. During the studies, visual acuity tests and funduscopy were repeated at week 52, week 104, and at the end-of-treatment visit.

*The applicant states that baseline assessments are not overly rigorous or systematic in nature, especially for evaluating disease progression thereby limiting conclusions.*

## PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

Albiglutide vs. Placebo

As detailed in Table 71 , subjects receiving albiglutide had a higher incidence of diabetic retinopathy events compared to placebo (3.6 % vs. 1.7%, respectively). In the albiglutide arm most cases were of background retinopathy 86% (32 of 37). In the placebo group all subjects with an on-therapy AE of retinopathy had background retinopathy.

Albiglutide vs. All comparators

As described in Table 71 the proportion of subjects with investigator identified diabetic retinopathy were similar between the albiglutide and the all comparators groups (3.4% for both groups). The majority of subjects had baseline retinopathy and a small proportion had proliferative retinopathy.

There were no retinopathy related SAEs or withdrawals.

**Table 71: On-therapy Investigator-Identified Diabetic Retinopathy Events (P3-ISP)**

Description	Albiglutide vs. All Comparators				Albiglutide vs . Placebo			
	All Comparators (N=2284)		Albiglutide (N=2116)		Placebo (N=468)		Albiglutide (N=923)	
	n (%)	Num. of AEs	n (%)	Num. of AEs	n (%)	Num. of AEs	n (%)	Num. of AEs
<b>On-therapy Diabetic Retinopathy Events</b>								
Any AE	87 (3.8)	98	83 (3.9)	93	10 (2.1)	10	36 (3.9)	38
Diabetic retinopathy	77 (3.4)	82	71 (3.4)	75	8 (1.7)	8	33 (3.6)	34
Retinopathy	6 (0.3)	6	6 (0.3)	7	2 (0.4)	2	2 (0.2)	3
Macular edema								
<b>Severity</b>								
Background DR	74 (3.2)	81	74 (3.5)	79	10 (2.1)	10	32 (3.5)	33
Proliferative DR	13 (0.6)	17	12 (0.6)	14	0	0	5 (0.5)	5
<b>Treatment</b>								
No treatment	12 (0.5)	14	7 (0.3)	7	N/A	N/A	3 (0.3)	3
Laser Photocoagulation	2 (0.1)	2	6 (0.3)	7	N/A	N/A	2 (0.2)	2
Vitrectomy	1 (0.0)	1	0	0	N/A	N/A	0	0

Adapted from ISS Table 165 page 503. AEs= adverse events

**Reviewer Comment:** *In the clinical program subjects with active proliferative retinopathy were excluded from participation in the study. Since the vast majority of subjects with on-therapy retinopathy had background retinopathy the sponsor was asked to clarify the proportion of subjects with retinopathy at baseline who developed background retinopathy on albiglutide. The applicant noted that 16 % ( n=11/70) of albiglutide-treated subjects with on-therapy diabetic*

**retinopathy events and 13% (n=10/76) among subjects in the all comparators group had a prior history of diabetic retinopathy documented in specific retinopathy eCRFs. The number of subjects with on-therapy events who met baseline diabetic retinopathy criteria were balanced between events of proliferative and background severity.**

#### Dose effects

Evaluation of a relationship between dose effect and the development of diabetic retinopathy was evaluated in the forced up-titration study and 4 optional titration studies.

#### Forced Uptitration Studies

Study GLP112756 is a randomized, double blind designed to evaluate the efficacy and safety of 30 mg and 50 mg doses of albiglutide. Subjects were forced up titrated to the 50 mg dose at 12 weeks.

As demonstrated in Table 72, there was a higher incidence of on-therapy retinopathy in albiglutide treated subjects compared with placebo. Subject receiving 30 mg had a higher incidence and event rate compared to 50 mg. However, the overall numbers of events were small.

**Table 72: On-Therapy Adverse Events Occurring in More Than 2% of Subjects in Either Albiglutide Treatment Group - Overall Data (Safety Population Study GLP112756)**

System organ class Preferred term	Placebo (N=101) n (%)		Albiglutide 30 mg Weekly (N=101) n (%)		Albiglutide 50 mg Weekly (N=99) n (%)	
	n (%)	# AEs / Rate <sup>1</sup>	n (%)	#AEs / Rate <sup>1</sup>	n (%)	#AEs / Rate <sup>1</sup>
<b>Eye Disorders</b>						
Any event	5 (5.0)	6 / 3.00	14 (13.9)	19 / 8.68	10 (10.1)	10 / 5.23
Diabetic retinopathy	1 (1.0)	1 / 0.50	4 (4.0)	4 / 1.83	1 (1.0)	1 / 0.52
Vision blurred	0	0	1 (1.0)	1 / 0.46	4 (4.0)	4 / 2.09

Adapted from CSR GLP112756 Table 40 page 138.

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 is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the treatment period being summarized.

**Reviewer Comment: The overall number of diabetic retinopathy events were too few to make any assessment of a dose effect.**

#### Optional Up-titration Studies

On-therapy retinopathy events in subjects in the optional titrations studies (GLP108486, GLP112753, GLP112754, and GLP112757) are summarized in Table 73. Subjects who experienced persistent hyperglycemia were eligible for dose titration or hyperglycemia rescue as per the protocol. Of the 1362 albiglutide treated subject 69% (940/ 1362 subjects titrated up to the 50 mg dose.

The data suggests that subjects who up titrated to the 50 mg dose had a higher incidence of diabetic retinopathy events compared to albiglutide 30 mg (5% vs. 2.1%, respectively). When adjusted for exposure the AE density was slightly higher in the 50 mg group, 2.76 events/100 person years vs. 1.61 events/ 100 person years in the 30 mg group.

**Table 73 On-therapy Retinopathy Events by Actual Titration Experience –Optional Titration Studies (P3-ISP)**

Eye Disorder SOC Preferred Term	Albiglutide 30 mg (N=422)		Albiglutide 50 mg (N=940)		Albiglutide 50 mg <sup>1</sup>			
	n (%)	#AEs/ Density	n (%)	#AEs/ Density	Prior to Titration		After Titration	
					n (%)	#AEs / Density	n (%)	#AEs / Density
Any event	53 (12.6)	67/ 11.95	143 (15.2)	199 / 10.99	48 (5.1)	63 / 11.32	103 (11.0)	136 / 10.84
Diabetic retinopathy	9 (2.1)	9 / 1.61	47 (5.0)	50 / 2.76	9 (1.0)	9 / 1.62	38 (4.0)	41 / 3.27
Retinopathy	1 (0.2)	1 / 0.18	7 (0.7)	7 (0.39)	1 (0.1)	1 / 0.18	6 (0.6)	6 / 0.48
Retinopathy hypertensive	0	0	2 (0.2)	2 / 0.11	1 (0.1)	1 / 0.18	1 (0.1)	1 / 0.08

Source Data: ISS Table 166 page 506 1 AE = adverse event; SOC = System Organ Class.

Note: Subjects receiving albiglutide are summarized according to their actual titration experience. On-therapy events are 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. For each level of summarization, a subject was counted once if the subject reported 1 or more events. Percentages are based on the number of subjects in each treatment grouping. The system organ class (SOC) and the preferred term within the SOC are

presented by decreasing frequency of incidence for the combined albiglutide treatment groupings.

1 Num. of AEs = the total number of AEs at each level of summarization.

Density per 100 person-years = 100 \* (number of AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment grouping during the treatment period being summarized. 2 Subjects who titrated to 50 mg albiglutide had their AEs classified as prior to titration or after titration. The incidence density calculations split the cumulative study treatment exposure into prior to titration (30 mg) and after titration (50 mg) exposure durations

**Reviewer Comment: Interpretation of data from the optional up-titration studies is limited by the fact that subjects who up titrated had poorer glycemic control which itself is risk factor for the development of retinopathy.**

#### 4MSU DIABETIC RETINOPATHY

Additional diabetic retinopathy data was not provided with the update.

Renal Study: Overall 14 subjects (47%) in the albiglutide group and 16 subjects (53%) in the sitagliptin group experienced on-therapy diabetic retinopathy events. Baseline previous clinical diagnosis of diabetic retinopathy was similar between treatment arms and most cases of on-therapy retinopathy in the albiglutide group were non-proliferative.

## CARDIOVASCULAR SAFETY

The CV meta-analysis was conducted for the Major Adverse Cardiovascular Events Plus (MACE-plus). This was a composite endpoint consisting of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina.

The sponsor had (b) (4)  
 the key endpoints for assessment of CV risk to use MACE-plus hospitalization for unstable angina (MACE+). This composite endpoint is consistent with the FDA guidance.

The primary objective of this meta-analysis was to evaluate whether albiglutide alters the risk of CV events in subjects with T2DM relative to all comparators. The secondary objective of this meta-analysis was to evaluate separately the albiglutide CV risk relative to active comparators plus background therapy and placebo plus background therapy.

Methods: CV safety data was prospectively collected in a blinded manner for adjudication by an independent Clinical Endpoint Committee (CEC). Data were included from 9 studies: 8 Phase III studies and one Japanese Phase IIb (Study GLP110932) study of short 16-week duration.

The CEC consisted of 5 physicians: 3 cardiologists, 1 physician trained in stroke medicine and diabetic medicine, respectively. With the exception of possible cerebrovascular events, each suspected event was reviewed independently by the pair of CEC cardiologists (which did not include the CEC chairman). The pair entered their adjudication decisions independently into Global View Event Net (event adjudication management system). For each event where the reviewers agreed on a classification, the event was deemed classified and adjudicated. Mismatches were highlighted for adjudication at a scheduled CEC meeting. All 5 members attended the CEC meetings and the cases were adjudicated by consensus. For cerebrovascular events, each suspected event was reviewed by the full CEC.

Other events adjudicated by the CEC (that were not endpoints), included silent (clinically unrecognized) MIs, hospitalizations for other angina, hospitalizations for other chest pain, hospitalizations for heart failure, subdural/extradural hemorrhages, and non-CV deaths. In addition, the CEC reviewed all transient ischemic attacks and coronary

revascularizations to check for any missed stroke, MIs, or unstable angina events. The CEC also reviewed all serious adverse events to check for any missed MACE+ events.

As noted in Dr. Li's review the pre-specified primary analysis was a time-to-event analysis based on a Cox proportional hazards model stratified by trial that included all primary events observed during the studies. A group sequential testing strategy was pre-specified to control the overall Type I error rate to demonstrate albiglutide did not exhibit an excess amount of risk relative to comparators with a hazard ratio (HR) risk margin of 1.8 based on the MACE+ primary CV endpoint.

As described in Dr. Li's review among the 5,107 subjects in the CV safety analysis population, 44 of 2,524 albiglutide subjects had an event that was adjudicated as the primary composite endpoint, while 47 of 2,583 comparator subjects experienced the primary endpoint events. Based on the primary analysis model, the hazard ratio estimate of albiglutide versus comparator is 0.93 with corresponding 97.55% CI (0.55, 1.58). This meets the FDA requirements for filing and approval.

Dr. Li notes that at the time of the BLA submission there was an imbalance in events pending adjudication in the groups (7 in albiglutide group and 1 in all comparators group). To study the impact of this imbalance in pending adjudication, Dr. Li calculated the M-H estimate of the overall risk ratio under a worst case scenario assuming all pending events in albiglutide group would be adjudicated as MACE+ and none in comparators group. The Mantel-Haenszel risk ratio (M-H RR) was 1.07 with 97.55% CI (0.69, 1.65).

Please refer to Dr. Bo Li's review of the cardiovascular (CV) meta-analysis for a full discussion.

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

#### Albiglutide vs. Placebo

Adverse events reported in at least 2% of subjects in either treatment group are presented in Table 74. The overall frequency of occurrence was balanced between arms; 85.5% (789/923) for albiglutide and 82.3% (n=385/468) for placebo. Common adverse events that occurred in >5% of albiglutide subjects are highlighted in Table 74. An imbalance (>2% difference) in events not favoring albiglutide occurred for events of diarrhea, nausea, injection site reaction, diabetic retinopathy and influenza.

The two most common preferred terms associated with a treatment emergent adverse event in the albiglutide group and placebo arm were upper respiratory tract infection

(14.2 %, 131/923 and 13%, 61/486, respectively) and diarrhea (13.1%, 121/923 and 10.5% 49/468, respectively). The greatest imbalance between groups was driven by injection site reactions with 10.5% (97/923) of albiglutide treated subject experiencing an ISR compared to 2.1% (10/468) of placebo treated subjects.

**Table 74: On-therapy Adverse Events Occurring in More Than 2% of Subjects in Either Treatment Group (Albiglutide vs. Placebo)**

Preferred Term	Placebo (N=468)		Albiglutide (N=923)	
	n (%)	Number of AEs/Density <sup>1</sup>	n (%)	Number of AEs/Density <sup>1</sup>
Any event	385 (82.3)	2419 / 287.73	789 (85.5)	5480 / 305.41
<b>Upper respiratory tract infection</b>	<b>61 (13.0)</b>	<b>88 / 10.47</b>	<b>131 (14.2)</b>	<b>169 / 9.42</b>
<b>Diarrhea</b>	<b>49 (10.5)</b>	<b>62 / 7.37</b>	<b>121 (13.1)</b>	<b>168 / 9.36</b>
<b>Nausea</b>	<b>45 (9.6)</b>	<b>53 / 6.30</b>	<b>102 (11.1)</b>	<b>145 / 8.08</b>
<b>Injection site reaction</b>	<b>10 (2.1)</b>	<b>85 / 10.11</b>	<b>97 (10.5)</b>	<b>630 / 35.11</b>
<b>Nasopharyngitis</b>	<b>47 (10.0)</b>	<b>61 / 7.26</b>	<b>86 (9.3)</b>	<b>115 / 6.41</b>
<b>Hypertension</b>	<b>38 (8.1)</b>	<b>43 / 5.11</b>	<b>75 (8.1)</b>	<b>80 / 4.46</b>
<b>Headache</b>	<b>44 (9.4)</b>	<b>58 / 6.90</b>	<b>71 (7.7)</b>	<b>90 / 5.02</b>
<b>Cough</b>	<b>29 (6.2)</b>	<b>35 / 4.16</b>	<b>64 (6.9)</b>	<b>75 / 4.18</b>
<b>Urinary tract infection</b>	<b>33 (7.1)</b>	<b>48 / 5.71</b>	<b>63 (6.8)</b>	<b>81 / 4.51</b>
<b>Back pain</b>	<b>27 (5.8)</b>	<b>36 / 4.28</b>	<b>62 (6.7)</b>	<b>68 / 3.79</b>
<b>Arthralgia</b>	<b>30 (6.4)</b>	<b>36 / 4.28</b>	<b>61 (6.6)</b>	<b>83 / 4.63</b>
<b>Sinusitis</b>	<b>27 (5.8)</b>	<b>37 / 4.40</b>	<b>57 (6.2)</b>	<b>71 / 3.96</b>
<b>Bronchitis</b>	<b>35 (7.5)</b>	<b>43 / 5.11</b>	<b>55 (6.0)</b>	<b>64 / 3.57</b>
<b>Influenza</b>	<b>15 (3.2)</b>	<b>17 / 2.02</b>	<b>48 (5.2)</b>	<b>55 / 3.07</b>
Constipation	24 (5.1)	28 / 3.33	42 (4.6)	46 / 2.56
Pain in extremity	24 (5.1)	27 / 3.21	42 (4.6)	46 / 2.56
Dizziness	22 (4.7%)	22 / 2.62	39 (4.2%)	42 / 2.34
Musculoskeletal pain	22 (4.7%)	25 / 2.97	39 (4.2%)	45 / 2.51
Edema peripheral	24 (5.1)	25 / 2.97	39 (4.2)	42 / 2.34
Vomiting	12 (2.6%)	12 / 1.43	39 (4.2%)	52 / 2.90
Fatigue	20 (4.3%)	21 / 2.50	35 (3.8%)	37 / 2.06
Pharyngitis	25 (5.3)	32 / 3.81	34 (3.7)	39 / 2.17
Gastroenteritis	12 (2.6)	12 / 1.43	33 (3.6)	38 / 2.12
Abdominal pain	17 (3.6)	19 / 2.26	33 (3.6)	37 / 2.06
Diabetic retinopathy	8 (1.7)	8 / 0.95	33 (3.6)	35 / 1.95
Anemia	19 (4.1)	21 / 2.50	33 (3.6)	34 / 1.89
Gastroesophageal reflux disease	9 (1.9)	11 / 1.31	32 (3.5)	35 / 1.95
Dyspepsia	13 (2.8)	16 / 1.90	31 (3.4)	35 / 1.95
Muscle spasms	15 (3.2)	15 / 1.78	26 (2.8)	30 / 1.67
Cataract	11 (2.4)	11 / 1.31	26 (2.8)	26 / 1.45
Anxiety	11 (2.4)	11 / 1.31	26 (2.8)	30 / 1.67
Depression	15 (3.2)	15 / 1.78	26 (2.8)	26 / 1.45
Insomnia	10 (2.1)	10 / 1.19	26 (2.8)	29 / 1.62
Osteoarthritis	16 (3.4)	17 / 2.02	25 (2.7)	29 / 1.62
Vertigo	6 (1.3)	9 / 1.07	24 (2.6)	25 / 1.39
Contusion	13 (2.8)	15 / 1.78	23 (2.5)	27 / 1.50
Rash	10 (2.1)	10 / 1.19	23 (2.5)	25 / 1.39
Neuropathy peripheral	7 (1.5)	7 / 0.83	20 (2.2)	23 / 1.28

Injection site hematoma	10 (2.1)	18 / 2.14	19 (2.1)	23 / 1.28
Hypoesthesia	5 (1.1)	5 / 0.59	19 (2.1)	19 / 1.06
Oropharyngeal pain	9 (1.9)	12 / 1.43	19 (2.1)	20 / 1.11
Dyslipidemia	14 (3.0)	15 / 1.78	19 (2.1)	20 / 1.11
Cellulitis	10 (2.1)	10 / 1.19	18 (2.0)	20 / 1.11
Gastritis	10 (2.1)	12 / 1.43	18 (2.0)	21 / 1.17
Myalgia	10 (2.1)	13 / 1.55	18 (2.0)	20 / 1.11
Sinus congestion	6 (1.3%)	7 / 0.83	18 (2.0%)	20 / 1.11
Abdominal pain upper	12 (2.6)	14 / 1.67	17 (1.8)	18 / 1.00
Chest pain	16 (3.4)	17 / 2.02	17 (1.8)	18 / 1.00
Tooth abscess	11 (2.4)	12 / 1.43	16 (1.7)	18 / 1.00
Ligament sprain	10 (2.1)	13 / 1.55	16 (1.7)	17 / 0.95
Muscle strain	14 (3.0)	16 / 1.90	14 (1.5)	14 / 0.78
Benign prostatic hyperplasia	10 (2.1)	10 / 1.19	3 (0.3)	3 / 0.17

ISS Table 51 page 175. 1. Number of AEs = the total number of AEs at each level of summarization. Density per 100 person-years = 100 \* (number of AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the treatment period being summarized.

### Albiglutide vs. All Comparators

Adverse events reported in at least 2% of subjects in either treatment group are presented in Table 75. The overall incidence of treatment emergent events was slightly higher in the albiglutide arm 83.5% (1766/2116) vs all comparators 80.6% (1840/2284). Common adverse events that occurred in >5% of albiglutide subjects are highlighted in Table 75. An imbalance (>2% difference) in events not favoring albiglutide occurred for events of diarrhea and injection site reactions. The two most common preferred terms associated with a treatment emergent adverse events in the albiglutide group were upper respiratory tract infection and diarrhea (12.9%, 274/2116 and 12.9%, 272/2116). The greatest imbalance between groups was driven by injection site reactions, with 8.8% (187/2116) of albiglutide treated subject experiencing an ISR compared to 2.0% (45/2284) of all comparators.

**Table 75: On-therapy Adverse Events Occurring in More Than 2% of Subjects in Either Treatment Group (Albiglutide vs. All Comparators)**

Proffered Term	All Comparators N=2284	Number of AEs/Density <sup>1</sup>	Albiglutide 2116	Number of AEs/Density <sup>1</sup>
Any event	1840(80.6%)	10076/227.6	1766(83.5%)	11042/327.6
<b>Upper respiratory tract infection</b>	<b>256 (11.2)</b>	<b>337 / 9.29</b>	<b>274 (12.9)</b>	<b>345 / 10.24</b>
<b>Diarrhea</b>	<b>209 (9.2)</b>	<b>273 / 7.52</b>	<b>272 (12.9)</b>	<b>374 / 11.10</b>
<b>Nausea</b>	<b>242 (10.6)</b>	<b>283 / 7.80</b>	<b>243 (11.5)</b>	<b>351 / 10.42</b>
<b>Nasopharyngitis</b>	<b>209 (9.2)</b>	<b>273 / 7.52</b>	<b>190 (9.0)</b>	<b>248 / 7.36</b>
<b>Injection site reaction</b>	<b>45 (2.0)</b>	<b>142 / 3.91</b>	<b>187 (8.8)</b>	<b>1171 / 34.75</b>
<b>Urinary tract infection</b>	<b>187 (8.2)</b>	<b>254 / 7.00</b>	<b>156 (7.4)</b>	<b>196 / 5.82</b>
<b>Headache</b>	<b>181 (7.9)</b>	<b>228 / 6.28</b>	<b>156 (7.4)</b>	<b>190 / 5.64</b>
<b>Hypertension</b>	<b>165 (7.2)</b>	<b>180 / 4.96</b>	<b>156 (7.4)</b>	<b>166 / 4.93</b>
<b>Sinusitis</b>	<b>111 (4.9)</b>	<b>145 / 4.00</b>	<b>130 (6.1)</b>	<b>157 / 4.66</b>
<b>Back pain</b>	<b>140 (6.1)</b>	<b>160 / 4.41</b>	<b>125 (5.9)</b>	<b>133 / 3.95</b>
<b>Bronchitis</b>	<b>147 (6.4)</b>	<b>173 / 4.77</b>	<b>123 (5.8)</b>	<b>144 / 4.27</b>

<b>Arthralgia</b>	<b>135 (5.9)</b>	<b>161 / 4.44</b>	<b>122 (5.8)</b>	<b>154 / 4.57</b>
<b>Cough</b>	<b>134 (5.9)</b>	<b>162 / 4.46</b>	<b>115 (5.4)</b>	<b>132 / 3.92</b>
Vomiting	101 (4.4)	117 / 3.22	104 (4.9)	147 / 4.36
Constipation	87 (3.8)	96 / 2.65	100 (4.7)	108 / 3.21
Influenza	106 (4.6)	139 / 3.83	96 (4.5)	108 / 3.21
Dyspepsia	58 (2.5)	65 / 1.79	80 (3.8)	94 / 2.79
Pain in extremity	104 (4.6)	126 / 3.47	80 (3.8)	87 / 2.58
Edema peripheral	136 (6.0)	146 / 4.02	79 (3.7)	84 / 2.49
Dizziness	84 (3.7)	99 / 2.73	79 (3.7)	90 / 2.67
Fatigue	61 (2.7)	68 / 1.87	74 (3.5)	77 / 2.29
Musculoskeletal pain	72 (3.2)	80 / 2.20	73 (3.4)	81 / 2.40
Gastroenteritis	72 (3.2)	79 / 2.18	69 (3.3)	79 / 2.34
Diabetic retinopathy	76 (3.3)	82 / 2.26	70 (3.3)	73 / 2.17
Cataract	68 (3.0)	72 / 1.98	66 (3.1)	70 / 2.08
Gastro esophageal reflux disease	47 (2.1)	54 / 1.49	64 (3.0)	69 / 2.05
Abdominal pain	59 (2.6)	64 / 1.76	60 (2.8)	65 / 1.93
Pharyngitis	74 (3.2)	88 / 2.43	55 (2.6)	62 / 1.84
Anemia	83 (3.6)	87 / 2.40	56 (2.6)	61 / 1.81
Osteoarthritis	60 (2.6)	75 / 2.07	52 (2.5)	58 / 1.72
Injection site hematoma	63 (2.8)	109 / 3.00	53 (2.5)	67 / 1.99
Anxiety	43 (1.9)	44 / 1.21	53 (2.5)	57 / 1.69
Muscle spasms	49 (2.1)	54 / 1.49	49 (2.3)	53 / 1.57
Rash	50 (2.2)	53 / 1.46	45 (2.1)	48 / 1.42
Depression	56 (2.5)	59 / 1.63	45 (2.1)	47 / 1.39
Insomnia	48 (2.1)	48 / 1.32	44 (2.1)	47 / 1.39
Decreased appetite	48 (2.1)	48 / 1.32	43 (2.0)	45 / 1.34
Contusion	59 (2.6)	71 / 1.96	40 (1.9)	47 / 1.39
Cellulitis	49 (2.1)	52 / 1.43	34 (1.6)	46 / 1.37
Dyslipidemia	46 (2.0)	49 / 1.35	34 (1.6)	35 / 1.04
Chest pain	52 (2.3)	56 / 1.54	28 (1.3)	30 / 0.89

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- At week 26, the most common on-therapy AEs (by PT) for both the albiglutide and all comparators groups were: diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, and headache. An additional common AE in the albiglutide group was for injection site reactions.
- At Week 52, the most common on-therapy AEs for both the albiglutide and all comparators groups were: upper respiratory tract infection, nasopharyngitis, urinary tract infection, diarrhea, nausea, and headache. An additional common AE in the albiglutide group was injection site reactions.

#### RENAL STUDY (GLP114130) COMMON ADVERSE EVENTS

The most common preferred terms occurring in > 5% of albiglutide treated subjects with a higher frequency of occurrence compared to sitagliptin were for events of diarrhea, urinary tract infection, constipation, and peripheral edema. The greatest imbalances

among these events not in favor of albiglutide were for events of diarrhea and constipation.

**Table 76: On-Therapy Adverse Events Occurring in More Than 2% of Subjects with a higher number in the albiglutide group.**

System Organ Class Preferred Term	Sitagliptin (N=246)		Albiglutide (N=249)	
	n (%)	Number of AEs/Rate <sup>1</sup>	n (%)	Number of AEs/Rate <sup>1</sup>
Any on-therapy AE	200 (80.3)	881 /	198 (80.5)	788 / 330.59
<b>Urinary tract infection</b>	<b>23 (9.2)</b>	<b>28 / 11.03</b>	<b>20 (8.1)</b>	<b>27 / 11.33</b>
Bronchitis	9 (3.6)	9 / 3.55	7 (2.8)	10 / 4.20
Influenza	8 (3.2)	9 / 3.55	7 (2.8)	9 / 3.78
<b>Diarrhea</b>	<b>25 (10.0)</b>	<b>30 / 11.82</b>	<b>16 (6.5)</b>	<b>21 / 8.81</b>
<b>Constipation</b>	<b>15 (6.0)</b>	<b>16 / 6.30</b>	<b>6 (2.4)</b>	<b>6 / 2.52</b>
Nausea	12 (4.8)	14 / 5.52	8 (3.3)	19 / 7.97
Hemorrhoids	6 (2.4)	6 / 2.36	3 (1.2)	4 / 1.68
Pain in extremity	7 (2.8)	8 / 3.15	4 (1.6)	5 / 2.10
<b>Edema peripheral</b>	<b>14 (5.6)</b>	<b>15 / 5.91</b>	<b>8 (3.3)</b>	<b>8 / 3.36</b>
Injection site reaction	10 (4.0)	70 / 27.58	1 (0.4)	1 / 0.42
Dizziness	8 (3.2)	9 / 3.55	5 (2.0)	5 / 2.10
Renal failure	12 (4.8)	15 / 5.91	11 (4.5)	16 / 6.71
Diabetic retinopathy	12 (4.8)	13 / 5.12	9 (3.7)	9 / 3.78
Cataract	9 (3.6)	9 / 3.55	5 (2.0)	5 / 2.10
Gout	11 (4.4)	12 / 4.73	7 (2.8)	7 / 2.94
Hyperuricaemia	8 (3.2)	9 / 3.55	3 (1.2)	3 / 1.26
Hyperkalaemia	7 (2.8)	12 / 4.73	2 (0.8)	2 / 0.84

Source: Modified CSR GLP114130 Table 46 Page 156.

1. Number of AEs = 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 is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the treatment period being summarized.

### Adverse events occurring more frequently in the albiglutide arm

The applicant conducted an analysis of event terms in the albiglutide group that met criteria for frequency of  $\geq 2\%$ , and occurred more frequently in the albiglutide group (RR.1.25 and lower limit of the CI >0.8). Results of this analysis are depicted in Table 77. The applicant categorized adverse events that occurred more frequently in albiglutide treated subjects and were felt to have a potential causal relationship to albiglutide as adverse reactions.

Common adverse reactions were: diarrhea, nausea, injection site reactions, vomiting, constipation, dyspepsia, GERD, and hypoglycemia (particularly when used in combination with SU or insulin).

**Reviewer Comment: The applicant notes that the relative risk (RR) criteria employed above are a tool and does not represent a statistical analysis. Safety**

***data regarding diarrhea, vomiting and injections site reactions are presented in their respective sections under adverse events of special interest in section 7.3.5.***

**Table 77: On-therapy Adverse Events Occurring in  $\geq$  2% of Subjects and More Frequently in the Albiglutide Group (P3-ISP)**

AE Preferred Term	Placebo (N=468)		Albiglutide (N=923)	
	n (%)	Number of AEs/ Density <sup>1</sup>	n (%)	Number of AEs/ Density <sup>1</sup>
Diarrhea	49 (10.5)	62 / 7.37	121 (13.1)	168 / 9.36
Injection site reaction	10 (2.1)	85 / 10.11	97 (10.5)	630 / 35.11
Influenza	15 (3.2)	17 / 2.02	48 (5.2)	55 / 3.07
Vomiting	12 (2.6)	12 / 1.43	39 (4.2)	52 / 2.90
Diabetic retinopathy	8 (1.7)	8 / 0.95	33 (3.6)	35 / 1.95
Gastro esophageal reflux	9 (1.9)	11 / 1.31	32 (3.5)	35 / 1.95
Vertigo	6 (1.3)	9 / 1.07	24 (2.6)	25 / 1.39
Preferred Term	All Comparators (N=2284)		Albiglutide (N=2116)	
	n (%)	Number of AEs/ Density <sup>1</sup>	n (%)	Number of AEs/ Density
Diarrhea	209 (9.2)	273 / 7.52	272	374 / 11.10
Injection site reaction	45 (2.0)	142 / 3.91	187 (8.8)	1171 / 34.75
Constipation	87 (3.8)	96 / 2.65	100 (4.7)	108 / 3.21
Dyspepsia	58 (2.5)	65 / 1.79	80 (3.8)	94 / 2.79
Fatigue	61 (2.7)	68 / 1.87	74 (3.5)	77 / 2.29
Gastroesophageal reflux disease	47 (2.1)	54 / 1.49	64 (3.0)	69 / 2.05

SCS Table 23 and Table 24 – page 90-91

CI = confidence interval; HLT = high-level term; N/A = not applicable; RR = relative risk; SOC = system organ class. Note: Ontherapy AEs are 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. For each level of summarization, a subject was counted once if the subject reported 1 or more events. Percentages are based on the number of subjects in each treatment group. Hypoglycemic events are excluded from this table and are reported separately. The SOC, the HLT within the SOC, and the preferred term within the HLT are presented by decreasing proportions of subjects with AEs for the albiglutide group.

1. Number of AEs = the total number of AEs at each level of summarization. Density per 100 person-years =  $100 * (\text{number of AEs} / \text{person-years})$ , where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the treatment period being summarized.

Adverse reactions, occurring in  $<$ 2% of subjects were pneumonia, pancreatitis and atrial fibrillation/flutter.

In addition the applicant identified 2 additional preferred terms (pneumonia and atrial fibrillation and flutter) as adverse reactions due to the higher incidence of these events in the albiglutide arm with many of the events classified as serious (described in section 7.3.2. ). Atrial fibrillation and pneumonia events are discussed below.

### **Atrial fibrillation/flutter**

Cumulative data reveal an imbalance in on-therapy events of atrial fibrillation/ flutter occurring in 1.3% (27/2116) of subjects in the albiglutide treatment group compared to 0.6% (14/2284) in all comparators. In addition, many events were serious (12/33 in the albiglutide group and 4/11 events in comparators). However the overall event number was small and a determination of causality was confounded by underlying history of arrhythmia (7/25 subjects in the albiglutide group) and the presence of concurrent AEs at the time of events in many subjects.

In the renal study the incidence rate for atrial fibrillation/flutter was higher than in the P3-ISP [2.0% (5/249) in the albiglutide arm vs. 0.4 % (1/246) in sitagliptin arm]. Overall the majority of events occurred in men with mild to moderate renal impairment over 65 years of age.

#### **P3-ISP**

As depicted in both treatment comparison groupings in Table 78, preferred term events of atrial fibrillation/flutter occurred in a higher proportion of subject in the albiglutide arm as compared to placebo and all comparators. On-therapy events (serious and non-serious) of atrial fibrillation/ atrial flutter occurred in 25 subjects (30 events) in the albiglutide group and 11 subjects (12 events) in the all comparators grouping. There were no event related withdrawals. Nine albiglutide subjects (11 events) and 2 comparator subjects (3 events) experienced SAEs. SAEs of atrial fibrillation/ flutter occurred more frequently in the albiglutide group when compared to all comparators and are discussed in detail in Section 7.3.2

**Table 78: P3-ISP: Summary of Adverse Events in the Preferred Terms of Atrial Fibrillation and Atrial Flutter (overall data at week 104)**

Overall Total AEs Preferred Term	All comparator N=2284		Albiglutide N=2116	
	n (%)	No. AEs/density	n (%)	No. AEs/density
Atrial fibrillation	11 (0.48%)	12/0.33	22 (1.0%)	24/0.71
Atrial flutter	0	0	5 (0.2%)	6/0.18
<b>SAEs Preferred Term</b>				
Atrial fibrillation	2(0.1%)	3/0.08	9 (0.4%)	9/0.27
Atrial flutter	0	0	2 (0.1%)	2/0.06

Preferred Term	Placebo N=468		Albiglutide N=923	
	n (%)	No. AEs/density	n (%)	No. AEs/density
Atrial fibrillation	3 (0.6%)	3/0.36	7 (0.8%)	8/0.45
Atrial flutter	0	0	1 (0.1%)	1/0.06
SAEs Preferred Term				
Atrial fibrillation	0	0	0	0
Atrial flutter	0	0	0	0

Modified from ISS Table 203 & 203, Pages 613 – 615.

Baseline cardiovascular risk factors for the development of atrial fibrillation/flutter were balanced between the albiglutide and all comparators treatment arms.

Of the 25 subjects in the albiglutide group who had an arrhythmia event

- 7/25 had a prior history of arrhythmia
- 18/25 subjects did not have a history of arrhythmias, however in 12 subjects the arrhythmia event occurred with another concurrent adverse event that may have been contributory.

A dose dependency was not observed, of the 30 events in albiglutide subjects, 14 occurred at the 30 mg dose and 16 at the 50 mg dose.

Many of the atrial arrhythmia events (12/30 events) in the albiglutide program occurred in study GLP112754 (albiglutide vs. insulin glargine). There was an imbalance at baseline in prior history of arrhythmia (7.3% (37/504) vs. 3.7% (9/241) not in favor of albiglutide.

Overall, men were more likely to have an event of atrial fibrillation/flutter in both arms (68% (17/25) albiglutide vs. 73% (8/11) in comparators). The mean age for subjects developing an on-therapy arrhythmia in the albiglutide group was 66 years (mean age P3-ISP was 55 years). The majority of subjects had mild/moderate renal impairment (84% vs. 16% normal renal impairment in the P3-ISP). In addition 32% (8/25) of albiglutide treated subjects and 46% (5/11) of all comparators had a medical history of arrhythmia.

#### 4MSU - Atrial fibrillation

During the 4 month safety update period (0.2%, 3 events in 3 subjects) occurred for both the albiglutide and all comparators grouping. One event in each group was considered serious, and one subject treated with albiglutide who experienced a nonserious event discontinued treatment. Overall data was consistent with findings from the original BLA submission.

### Cumulative - Atrial fibrillation

On-therapy events of atrial fibrillation/ flutter occurred in 1.3% (27/2116) of subjects in the albiglutide treatment group (33 events, 0.83 events/100 person-years) and 0.6% (14/2284) in the all comparators treatment group (15 events, 0.35 events/100 person-years). In the albiglutide group 12 subjects (12 events) were serious and in the comparator group 3 subjects (3 events) were serious.

### Renal Study GLP114130- Atrial Fibrillation

There was a higher incidence of the atrial fibrillation/ flutter events in the albiglutide group (2.0% (5/249 subjects had 6 events) vs. 0.4 % in sitagliptin arm (1/246 subjects had 1 event). Of note, fewer subjects in the albiglutide arm had a history of arrhythmia when compared to sitagliptin [9.2%(23/249) vs. 13% (32/246), respectively). Similar to the P3-ISP the majority of subjects with an arrhythmia event were male and all events occurred in subjects with mild or moderate renal impairment.

The reviewer agrees with the applicant's plan to label events of atrial fibrillation and flutter and flutter in the adverse reactions. In addition atrial fibrillation and flutter should be followed as an event of special interest in the dedicated CV outcomes study and future studies with albiglutide.

### **Pneumonia:**

There were a higher proportion of subjects treated with albiglutide who developed on-therapy (serious and non-serious) events of pneumonia (1.8% (17/923) vs. placebo 0.6% (3/468). The overall incidence of on-therapy pneumonia was higher in the albiglutide group compared to all comparators (1.8%(37/2116) vs. 0.8% (18/2284), respectively. There was also a slightly higher proportion of lobar and primary atypical pneumonia in the albiglutide arm vs. all comparators. SAEs are discussed in Section 7.3.2.

**Table 79: P3-ISP: Non-Serious and Serious Events in the Lower Respiratory Tract Infection**

HLT Preferred Term	All Comparators (N=2284)		Albiglutide (N=2116)	
	n (%)	Number of events/ AE density <sup>1</sup>	n (%)	Number of events/ AE density <sup>1</sup>
Lower respiratory tract and lung infections	176 (7.7%)	221/ 6.1	166 (7.9%)	202/ 6.0
Bronchitis	147 (6.4%)	173/ 4.8	123 (5.8%)	144/ 4.2
Pneumonia	18 (0.8%)	19/ 0.5	37 (1.8%)	37/ 1.1
Lower respiratory tract infection	18 (0.8%)	26/ 0.7	12 (0.6%)	14/ 0.4
Lobar pneumonia	1 (0.0%)	1/ 0.3	3 (0.1%)	3/ 0.1
Bronchopneumonia	2 (0.1%)	2	2 (0.1%)	2/ 0.1
Pneumonia primary atypical	0	0	2 (0.1%)	2

HLT Preferred Term	Placebo (n=468)		Albiglutide (n=923)	
	n (%)	Number of events/ AE density	n (%)	Number of events/ AE density
Lower respiratory tract and lung infections	43 (9.12)	55/ 6.54	75 (8.1%)	90/ 0.87
Bronchitis	35 (7.5%)	43/ 5.11	55 (6.0%)	64/ 0.78
Pneumonia	3 (0.6%)	3/ 0.36	17 (1.8%)	17/ 0.95
Lower respiratory tract infection	7 (1.5%)	8/ 0.95	7 (0.8%)	9/ 0.50
Lobar pneumonia	1 (0.2%)	1/ 0.12	0	0

Source: ISS Table 212 and 213 page 630 -631. 1. Density = no. of AEs per 100 patient years

#### 4MSU - Pneumonia

During the incremental period for the 5 ongoing studies there were 10 subjects (0.7%) in the albiglutide treatment group with 10 on-therapy pneumonia events (sum of preferred terms pneumonia, lobar pneumonia and viral pneumonia). In the all comparator treatment group 11 subjects (0.7%) had 12 events of pneumonia. Five events in the albiglutide group and 4 in all comparators were SAEs. None of the events led to withdrawal of treatment. Two subjects in each treatment group reported a second event of pneumonia. In the albiglutide group Subject 3709753980 and Subject 3653755981 had both reported a second serious event during the study. All events occurred in anti-albiglutide antibody negative subjects.

#### Cumulative - Pneumonia

On-therapy events for pneumonia occurred in a higher frequency of albiglutide treated subjects (2.6%, 1.41 events/100 person-years) compared with all comparators (1.5%, 0.86 events/100 person-years). In total, pneumonia SAEs occurred for 16 subjects (0.8%) in the albiglutide treatment group (18 events) and 7 subjects (0.3%) in the all comparators treatment group (7 events). There were also 3 SAEs of bronchitis in the albiglutide treatment group versus none in the all comparators treatment group

Renal Study GLP114130: The incidence of pneumonia was 0.8% in the albiglutide treatment group (2 of 249 subjects, 2 events) and 1.6% in the sitagliptin group (4 of 246 subjects, 4 events). Note: there was also 1 report of necrotizing pneumonia in an albiglutide subject described in section 7.3.2.

#### **Transient ischemic attacks**

In the P3-ISP events of transient ischemic attacks were higher with albiglutide vs. all comparators (13 subjects (0.6%) vs. 5 subjects (0.2%), respectively). The overall incidence was balanced between albiglutide and the placebo group (5 albiglutide subjects, 0.5% vs. 2 placebo, and 0.4%).

The applicant states that one subject had a reported stroke after and one prior to the event of TIA. All subjects had an underlying history of cardiovascular disease. Seven events were SAEs and there were no withdrawals from events of TIAs.

Of the 13 subjects who received albiglutide over half were female (n=7) and the age ranged from 44 to 80 years. All had a history of cardiovascular disease. No TIAs led to withdrawal. Of the 13 events, 7 were SAEs

Of the 5 all comparator subjects with TIA, 1 had a history of stroke and the other subjects had underlying cardiovascular history.

In the Renal Phase III study there was 1 subject with an event of TIA in the sitagliptin arm compared to no events in the albiglutide arm

***Reviewer Comment: Adjudicated events for stroke and did not show a clinically relevant increased risk for albiglutide.***

#### **Psychiatric Disorders SOC**

A slightly higher proportion of albiglutide treated subjects (9%, 83/923) compared to placebo (8.1%, 38/468) had any event in the psychiatric disorders SOC. This small imbalance was also evident when albiglutide was compared to all comparators (7.47%, 158/2116) vs. (6.92, 158/2284).

As depicted in Table 80 events in the depressive disorders SOC were balanced. Albiglutide subjects had a higher incidence of suicidal and self-injurious behavior when compared to all comparators. As detailed in Table 80, 5 subjects in the albiglutide group and 1 in the all comparator group reported events of suicidal behaviors/intentional overdose.

**Table 80: P3-ISP: Suicidal depression behaviors/Intentional Overdose HLTs/PTs**

High Level Term Preferred Term	All Comparators n (%) / # SAE	Albiglutide (n=2116) n (%) / # SAE
<b>Any Event Psychiatric Disorders SOC</b>	158 (6.92)/ 5	158 (7.47)/ 7
<b>Depressive Disorders</b>	58 (2.54)/ 2*	47* (2.22)/ 2
<b>Suicidal and self-injurious Behavior</b>	1 (0.044)/ 0	4 (0.19)/ 2
<b>Mood alterations with depressive symptoms</b>	7 (0.37)/ 0	0
Intentional overdose	0	1** (0.047)/ 1
Accidental overdose	1 (0.044)/ 0	0

Source: SCS Table 60 page 190. \*includes 1 case of Depression with suicidal ideation (non-serious case classification) in the albiglutide group and 2 serious cases of Depression with suicidal ideation in the all comparators group. \*\*Case contains non-serious events of suicidal ideation and depression and is counted in each respective HLT

**Reviewer Comment: The overall numbers of events were small and an imbalance was not seen for depression and mood disorders. The applicant notes that individual case review identified 2 additional reports describing suicidal ideation occurring in SAE reports of depression, both in the all comparator group.**

#### 7.4.2 Laboratory Findings

Hematology, clinical chemistry, and urinalysis laboratory tests were performed at screening, and routine intervals as described in Appendix 1. Abnormalities were defined as laboratory values falling outside the upper and lower normal limits determined by the laboratory reference range. Abnormal laboratory results that crossed a pre-defined threshold were considered “of potential clinical concern” by the applicant.

Pancreatic enzymes, hepatic enzymes, serum GGT levels and serum calcitonin values of clinical concern are discussed separately under adverse events of special interest

## **Hematology**

Hematology parameters included basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils, platelets, red blood cell count, segmented neutrophils, and white blood cell count.

### Hematology P3-ISP

Overall there was no evidence of any clinically meaningful mean changes from baseline. Shifts from normal baseline for any of the hematology parameters across comparison groups were generally well balanced (ISS Table 235, 236 and 307). There did not appear to be a treatment related effect on hematology parameters.

### Hematology Renal Study

Clinically significant changes were observed in more albiglutide-treated subjects than sitagliptin-treated subjects for hematocrit (3.2%, 7/249 vs. 1.9%, 4/246) and hemoglobin (3.7, 8/249 vs. 1.5%, 3/246, respectively) values (CSR GLP114130 Table 74). However, subjects with clinically significant changes had abnormal values at baseline

## **Chemistry**

Chemistry parameters used in integrated summaries included: albumin, bicarbonate (carbon dioxide content), blood urea nitrogen, calcium, chloride, glucose, magnesium, phosphorus, potassium, sodium, total protein, uric acid, and serum creatinine.

### Chemistry P3-ISP

There was no evidence of any clinically meaningful mean changes from baseline for any of the general chemistry parameters across comparison groups. Although on-therapy shifts from normal baseline values were seen for most of the general chemistry and lipid chemistry parameters across the 3 comparison groups, the applicant notes that the majority of these shifts were not clinically significant.

### *Serum Creatinine*

Overall, in both the placebo and albiglutide groups, there were few shifts from normal baseline creatinine values to abnormal values and most shifts were not clinically significant. Overall, there were few shifts to low or high clinically significant values. At week 52 one subject shifted from normal baseline to high clinically significant (IAS Study report Table 269).

### *Liver function test*

Mean values for ALT, AST, alkaline phosphatase, bilirubin, and GGT were similar in the placebo and albiglutide groups. Overall there were small decreases in mean ALT and bilirubin values were observed over time in both groups to week 104. Consistent trends were not observed overtime in values for AST, alkaline phosphatase, GGT (ISS Table 247).

The applicant notes that changes in lipid levels were difficult to determine, as the use of lipid lowering drugs was not strictly controlled in the clinical program.

### Chemistry Renal GLP114130

#### *Serum Creatinine*

There were no creatinine shifts from baseline to abnormal clinically significant in either treatment group, and shifts from normal to abnormal not clinically significant were similar between the treatment groups (GLP114130 Table 14.3-2.7a). Shifts from baseline in renal impairment category were similar between the treatment groups (GLP 114130 CSR Table 81). There were no subjects with renal failure (eGFR < 15 mL/min/1.73 m<sup>2</sup>) at week 26. One subject (in the sitagliptin group) had moderate renal impairment at baseline that shifted to renal failure at Week 52.

#### *Liver enzymes*

Overall mean ALT, AST, GGT, and bilirubin values did not reveal any consistent treatment related trends. In this study ALT and AST test results up to 2.5 times the ULN and bilirubin up to 1.5 times the ULN were allowed at study entry.

***Reviewer Comment: Overall there were not many clinically significant changes across the albiglutide, all comparators and placebo treated groups with respect to change from baseline in hematology and chemistry parameters.***

### **Urine Parameters**

#### P3-ISP and Renal Study

No clinically relevant changes were seen in a change from baseline analysis of urinalysis parameters (study report: 14.3.4.5.1)

### **Urine Albumin/Creatinine Ratio**

Mean change from baseline of urine albumin/creatinine ratios were highly variable at each time point for the albiglutide versus all comparators and the albiglutide versus placebo comparison groups. Over time, the mean (SD) and median values in both

comparison groups showed small degrees of variability. Overall at week 104, 8.2% (23/282) subjects in the placebo group and 5.6%, 34/606 subjects in the albiglutide group shifted from normal baseline values to abnormal. (ISS Table 272)

Renal Study Median values for urine albumin/creatinine ratio decreased in both treatment groups and suggested no notable difference between the treatment groups

### **7.4.3 Vital Signs**

#### **BLOOD PRESSURE**

##### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

Mean changes in systolic and diastolic blood pressure varied within  $\pm 1$  mmHg over time in the albiglutide, placebo and active comparator groups. In those subjects not taking potentially confounding blood pressure lowering medication mean systolic blood pressure change from baseline at weeks 13 and 26 was within 1 mmHg of baseline values, and comparable in albiglutide-treated subjects compared with the all comparators group.

In study GLP112756, subjects underwent forced up-titration from 30 mg/week to 50 mg/week titration. There was not an albiglutide related dose response in blood pressure. Blood pressure changes from baseline in the 50 mg/week albiglutide group were comparable to the placebo group.

##### RENAL STUDY (GLP114130)

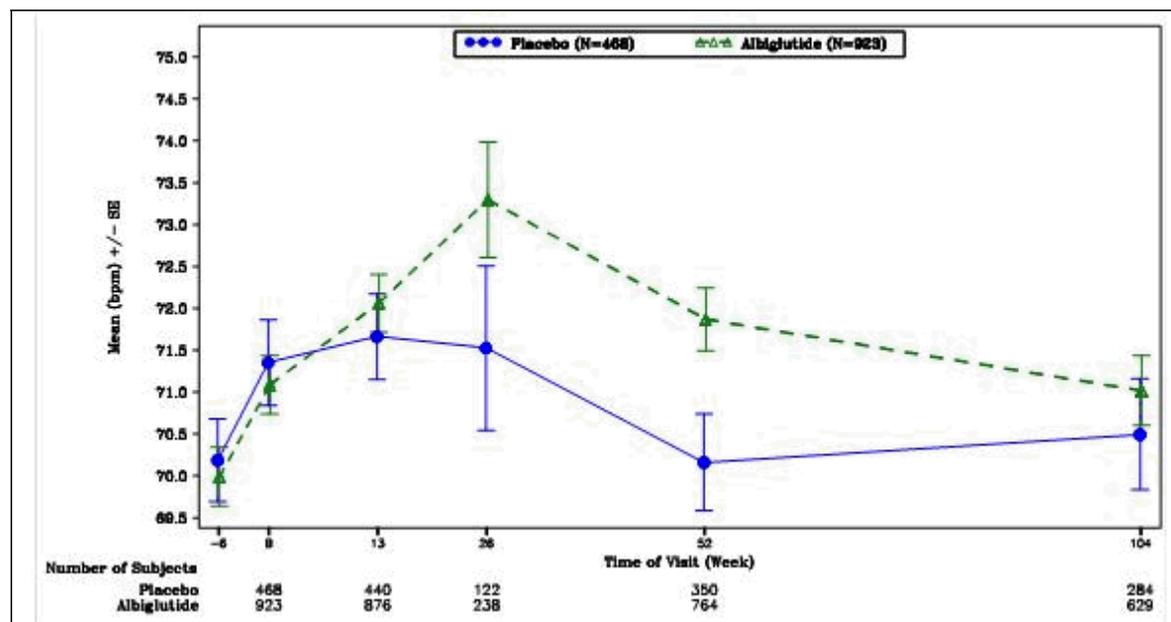
Overall, the changes from baseline in systolic blood pressure and diastolic blood pressure were similar between the albiglutide and sitagliptin treatment groups.

#### **HEART RATE**

Heart rate data was assessed by pulse rate and by digital ECGs. Mean heart rate derived from vital signs assessments were overall stable over time in the albiglutide and placebo arms, although mean heart rate was consistently higher (by 1-2 bpm), at each integrated analysis visit over time for the albiglutide group compared with placebo.

Mean heart rate changes from baseline derived from ECGs were numerically higher in the albiglutide group compared to placebo treated subjects See (treatment difference range of 0.8 to 1.4 bpm at weeks 13, 52 and 104).

**Figure 9 Mean Heart Rate Over Time From ECG Recordings for Albiglutide vs. Placebo Group (P3-ISP)**



Source : ISS Figure 64 Page 835 B=Baseline. ECG data at Week 26 contains fewer subjects because only two integrated studies GLP 114179 and GLP112756 collected ECG data between Week 13 and Week 52. Note: Final data through Week 104, partial data after Week 104.

Approximately 2.8% (n=26) of albiglutide-treated subjects had heart rate increases of >30 bpm compared with 1.5% (n=7) of placebo-treated subjects. A small number of <1.0% of albiglutide-treated subjects had on-therapy heart rate measurements of clinical concern with (<50 bpm or >120 bpm).

### Heart rate by dose

Up-titration from 30 to 50 mg resulted in a 1 to 2 bpm increase in heart rate (range 0.5 to 1.7 bpm). Heart rate measurements from vital signs showed no increase.

GLP112756 (Forced up-titration at week 12): In GLP112756, heart rate over time were assessed using 2 methods: by vital signs measurements and by analysis of triplicate ECG data. The Heart rate data from ECGs showed that albiglutide up-titration from 30 mg to 50 mg/week resulted in a transient 2 bpm heart rate increase observed at weeks 24 and 28 but not at Weeks 52 and 104.

Data from the integrated studies for albiglutide vs. all comparators group demonstrated that albiglutide up-titration from 30 mg to 50 mg/week resulted in an approximate 1-2 bpm increase in heart rate. Similarly for albiglutide vs. the placebo group, up-titration

from 30 mg to 50 mg/week also resulted in an approximate 1-2 bpm increase in heart rate (except at week 13).

Renal

There was a smaller percentage of subjects in the albiglutide treatment group compared with the sitagliptin group who experienced values of clinical concern on any on-therapy visit (2%, 5/249 vs. 5%, 12/246, respectively).

One subject in the albiglutide group, with mild renal impairment at baseline experienced a QTcF value at least 500 ms at the end-of-treatment. The change from baseline in eGFR for this subject was  $-20$  mL/min/1.73m<sup>2</sup>. There were no subjects in the sitagliptin group who experienced a QTcF value  $\geq 500$  ms at any on-therapy visit.

#### **7.4.4 Electrocardiograms (ECGs)**

##### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

The PR interval in subjects treated with albiglutide showed a small increase over all comparators ( $\leq 1$  msec) at week 52 and 104, and the RR interval showed larger decreases for albiglutide compare to all comparators.

QTcF values  $\geq 500$  msec or PR interval  $>300$  msec occurred in 1 albiglutide treated subject over the 2-year period.

QTcF change from baseline  $\geq 60$  msec occurred in  $<0.4\%$  of subjects treated with albiglutide and was comparable in placebo or active comparator groups

Up-titration to 50 mg albiglutide was not associated with any adverse change in ECG parameters.

##### RENAL STUDY (GLP114130)

ECG parameters were similar between treatment groups and did not show any consistent treatment-related trends in change from baseline.

##### TQT STUDY

The thorough QT Study was reviewed by the Interdisciplinary Review Team for QT Studies Consultation:

No significant QTc prolongation effect of albiglutide 30 mg and 50 mg was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean

difference between albiglutide 30 mg and 50 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines

#### 7.4.5 Special Safety Studies/Clinical Trials

Safety was determined in renal impairment and is discussed throughout this review as pertinent. Refer to Dr. Bo Li's review for discussion of the cardiovascular meta-analysis assessing cardiovascular safety of albiglutide.

#### 7.4.6 Immunogenicity

See relevant review in Section 6.1.11.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Dose response related AEs were primarily assessed in study GLP112765. The placebo controlled study design randomized subjects to albiglutide treatment arms of 30 mg only or 30 mg with forced uptitration to 50 mg (at week 12). Table 81 describes the dosing scheme in the P3-ISP.

**Table 81: Albiglutide Dosing in Phase 3 Integrated Studies**

Study Number	Albiglutide 30 mg only	Albiglutide 30→ 50 mg optional	Albiglutide 30→ 50 mg forced	Comparators
GLP112753		X		PBO, SU, DPP-IV
GLP112754		X		Insulin glargine(Lantus)
GLP112755	X			PBO
GLP112756	X		X	PBO
GLP112757		X		PBO, TZD
GLP108486		X		Prandial insulin
GLP114179			X	Liraglutide

Source: ISS Table 220, Page 646. DDP-IV=dipeptidyl peptidase-IV, PBO=placebo, SU=sulfonylurea, TZD=thiazolidinedione.

#### STUDY GLP112756

As detailed in Table 82, overall on-therapy events were similar between placebo, albiglutide 30 mg and albiglutide 50 mg (81.2 vs. 84.2 vs. 86.9%, respectively).

Three analyses were conducted by the applicant to evaluate dose response in the study.

First, the applicant compared overall data between the 30 mg and 50 mg up titrated dosing arms. Since many events in the 50 mg arm occurred during the first 12 weeks while subjects were still on 30 mg an analysis comparing the pre- and post-titration period in subjects in the 50 mg arm was conducted. Finally, the two treatment arms were compared in the post-titration period (weeks 12-52).

Overall, the proportion of subjects reporting on-therapy AEs through Week 104 were higher in the albiglutide 50 mg group (86.9% of subjects) compared to the albiglutide 30 mg (84.2%), and placebo groups (81.2%). Five common AEs occurred in a higher proportion of subjects with a higher AE density (number of AEs divided by person-years) in the 50 mg arm compared to the 30 mg and placebo arm. These events included: sinusitis, urinary tract infection, gastroesophageal reflux disease, injection site reaction and pain in the extremity. The greatest imbalance between doses occurred for preferred term events of ISR (2% placebo, 9.9% albiglutide 30mg an 18.2 % 50 mg dose).

**Table 82: On-therapy Adverse Events Occurring in at Least 5% of Subjects in Any Treatment Group by Random Treatment Assignment with a Higher Incidence and Density in 50 mg dose group (Study GLP112756 Safety Population)**

	Placebo (N=101)		Albiglutide 30 mg weekly (N=101)		Albiglutide 50 mg weekly (N=99)	
	n (%)	Number of AEs/Density <sup>1</sup>	n (%)	Number of AEs/Density <sup>1</sup>	n (%)	Number of AEs/Density <sup>1</sup>
<b>Any on-therapy event</b>	82 (81.2)	569/284.26	85 (84.2)	644/294.26	86 (86.9)	535/279.88
<b>Infections and Infestations</b>						
Sinusitis	6 (5.9)	7/3.50	6 (5.9)	6/2.74	7 (7.1)	10/5.23
Urinary tract infection	6 (5.9)	11/5.50	2 (2.0)	2/0.91	7 (7.1)	11/5.75
<b>Gastrointestinal disorders</b>						
Gastroesophageal reflux disease	2 (2.0)	4/2.00	2 (2.0)	2/0.91	5 (5.1)	5/2.62
<b>General disorders and administration site conditions</b>						
Injection site reaction	2 (2.0)	30/14.99	10 (9.9)	42/19.19	18 (18.2)	71/37.14
<b>Musculoskeletal and connective tissue disorders</b>						
Pain in extremity	3 (3.0)	3/1.50	6 (5.9)	6/2.74	7 (7.1)	7/3.66

Modified from ISS Table 221, Page 648. AE=adverse event.

Note: This table includes final data through Week 104 and partial data after Week 104. 1. Number of AEs=the total number of AEs at each level of summarization. Density per 100 person-years=100 \* where person-years was defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the treatment period being summarized.

The applicant further investigated dose effect by examining the incidence and event density of AEs in the 50 mg dose arm before and after up-titration and between week 12 and 52 post titration. The greatest imbalance pre and post titration was for events of

ISRs (3% vs. 15%, respectively). However among subjects who up titrated from 30 to 50 mg, the event rate for injection site reaction was lower in the post-titration period (40.4 pre-titration vs. 36.3 post-titration).

**Table 83: On-therapy Adverse Events Occurring in at Least 5% of Albiglutide-Treated Subjects in the Up-titration Group Before and After Titration by Random Treatment Assignment (Study GLP112756 Randomized Safety Population)**

	Albiglutide 50 mg weekly			
	Before Titration <sup>1</sup>		After Titration <sup>1</sup>	
	n (%)	Number of AEs/Density <sup>2</sup>	n (%)	Number of AEs/Density <sup>2</sup>
<b>Any on-therapy event</b>	53 (53.5)	121/488.62	73 (73.7)	414/248.81
<b>Infections and Infestations</b>				
Any Event	17 (17.2)	22/88.84	41 (41.4)	90/54.09
Sinusitis	2 (2.0)	2/8.0	6 (6.1)	8/4.8
Urinary tract infection	2 (2.0)	3/12.11	6 (6.1)	8/4.8
<b>Gastrointestinal disorders</b>				
Any event	14 (14.1)	20/80.76	28 (28.3)	48/28.85
GERD	1 (1)	1/4.04	4 (4)	4/2.4
<b>General disorders and administration site conditions</b>				
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
<b>Musculoskeletal and connective tissue disorders</b>				
Any event	6 (6.1)	10/40.38	19 (19.2)	30/18.03
Pain in extremity	1 (1.0)	1/4.0	6 (6.1)	6/3.6

Source: Integrated Analysis of Safety (ISS) Table SP3-33.9.13. AE=adverse event. 1. Subjects in the Albiglutide 50 mg treatment group had their AEs classified as prior to titration or after titration. The incidence density calculations split the cumulative study treatment exposure into prior to titration (30 mg) and after titration (50 mg) exposure durations. 2. Number of AEs=the total number of AEs at each level of summarization. Density per 100 person-years=100 \* (number of AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the group during the treatment period being summarized.

Evaluation of the period post-uptitration (week 12- week 52), demonstrated that a higher proportion of subjects in the 50 mg (12.5%) arm compared to 30 mg (8.2%) had an event of ISR. However, the event density was lower in the 50 mg arm (31.95/100 patient years versus 42.25/100 patient years).

### Gastrointestinal Events

GI events are a known adverse event of GLP-1 agonist use. The proportion of subjects with any GI event was similar across the 3 treatment groupings (35.6% for the placebo, 40.6% for 30-mg, albiglutide and 34.3% for 50 mg groups).

The most common events were diarrhea (reported in 14.9%/ density 9.94 of subjects in the placebo group, 11.9%/ density 8.68 of subjects in the albiglutide 30 mg group, 15.2%/ density 9.94 of subjects in the albiglutide 50 mg group, and) and nausea (9.9%/ density 5.0 for placebo, 13.9%/density 7.31 for albiglutide 30 mg, and 10.1%/density 8.37 for albiglutide 50 mg).

**Reviewer Comment; Review of dose response data from Study GLP112756 does not suggest a clear dose related adverse event signal.**

### Dose related Deaths, SAEs and AEWD

As delineated in Table 84, there were 4 deaths in albiglutide 50 mg group compared to none in the 30 mg group. Three subjects' deaths were due to cancer (including 1 pancreatic carcinoma), and 1 was due to drowning. AEs leading to withdrawal of active treatment were higher in the albiglutide 50 mg group (15.2%) compared with the albiglutide 30 mg (5.0%) and placebo (4.0%). However, the majority of withdrawals in the 50 mg arm were due ISRs (6/15 events) and single events in the Neoplasms SOC (5/15 events). In addition the sponsor states that 5 of the 15 subjects in the albiglutide 50 mg group were on the albiglutide 30 mg dose at the time of withdrawal. The incidence of severe AEs was higher in the albiglutide 50 mg group for the overall study, but the applicant states that many severe events occurred while those subjects were on the 30 mg dose.

**Table 84: Overview of Adverse Events Over Time by Dose (GLP112756 Safety Population)**

	Placebo (N=101)		Albiglutide 30 mg Weekly (N=101) n (%)		Albiglutide 50 mg Weekly (N=99) n (%)	
	n (%)	# of AEs <sup>1</sup>	n (%)	# of AEs <sup>1</sup>	n (%)	# of AEs <sup>1</sup>
<b>Any AE<sup>2</sup></b>	84 (83.2)	642	86 (85.1)	700	87 (87.9)	615
Any fatal AE	0	0	0	0	4 (4.0)	4
Any serious AE	13 (12.9)	19	14 (13.9)	21	16 (16.2)	20
Any AE leading to withdrawal	4 (4.0)	4	5 (5.0)	5	15 (15.2)	15
<b>Any AE by maximum intensity<sup>3</sup></b>						
Mild	30 (29.7)	453	29 (28.7)	486	20 (20.2)	398

Moderate	43 (42.6)	168	44 (43.6)	191	46 (46.5)	191
Severe	11 (10.9)	21	13 (12.9)	23	21 (21.2)	26
<b>On-therapy AE incidence rate<sup>4</sup></b>		284.26		294.26		279.88

Source: Modified ISS Table 224, Page 653. Note: Hypoglycemic events are excluded from this table except for serious adverse events (AEs). This table includes final data through Week 104 and partial data after Week 104.  
 1. Number of AEs=the total number of AEs at each level of summarization. 2. Unless otherwise stated, number of events in this table is for the pretherapy, on-therapy, and post therapy periods combined. 3. A subject was counted once according to the maximum intensity experienced if the subject reported 1 or more AEs. The AEs with missing intensity were considered severe in this summarization. 4. The ontherapy AE incidence rate per 100 person-years= $100 \times (\text{number of AEs} / \text{person-years})$ , where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the ontherapy treatment period.

### Dose response

Four P3 studies with optional up titration (Studies GLP108486, GLP112753, GLP112754, and GLP112757) were integrated to evaluate dose response. There were 940/1362 subjects (69.0%) treated with albiglutide who received the 50 mg dose. The mean time to up titration was 31.0 weeks (range: 8 to 133 weeks) with most up titrated by week 52. The adverse event of diabetic retinopathy had a higher incidence as well as density in the 50 mg group. Diabetic retinopathy pre-titration had an incidence of 1.0% (n=9), 1.62 AEs/100 person-years and diabetic retinopathy post-titration had an incident of 4.0% (n=38), 3.27 AEs/100 person-years.

***Reviewer Comment: Subjects who optionally up titrated may have had more progressive disease which is a risk factor for retinopathy and confounds causality assessment.***

### RENAL STUDY (GLP114130)

In the albiglutide group, approximately 57% of subjects (141 of 249) were up titrated to the 50-mg weekly dose of albiglutide. Approximately 32.1% had up titrated by week 26 and a further 22.1% by week 48.

The percentage of albiglutide subjects who experienced at least 1 AE was similar for subjects who received up titrated doses of albiglutide (79%) compared with those whose albiglutide doses were not up titrated (82%). The most frequently reported AEs were in the Infections and Infestations and GI Disorders SOCs. There was a higher incidence of upper respiratory tract infections in the up titrated group (7.8, 11/141) vs. 2.8%, 3/108 in subjects who did not up titrate. Dose up titration did not appear to exacerbate GI symptoms. The incidence of GI events (diarrhea, nausea, or vomiting) did not increase after up titration.

### **7.5.2 Time Dependency for Adverse Events**

At week 26, the most common on-therapy AEs by preferred term for both the albiglutide and all comparators groups were: diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, and headache. An additional common AE in the albiglutide group was ISR.

At Week 52, the most common on-therapy AEs for both the albiglutide and all comparators groups were: upper respiratory tract infection, nasopharyngitis, urinary tract infection, diarrhea, nausea, and headache. An additional common AE in the albiglutide group was ISR.

Over one-half of SMQ-identified systemic allergic reaction events occurred by week 26 (23 of 39 events in the albiglutide group and 18 of 34 events in the all comparators group).

GLP-1R agonists have shown increased rates of nausea and vomiting in the first months after initiation. In both the albiglutide and placebo treatment arms the majority of subjects reporting GI AEs (69% of albiglutide-treated subjects and 63% of placebo-treated subjects) occurred within the first 26 weeks. The number of nausea events at week 26 comprised approximately 70% of the nausea AEs reported during the overall study period (albiglutide group: 105/145 events at week 26 vs. 39/53 events for placebo). Diarrhea and nausea, showed a similar pattern with the majority of events occurring within the first 26 weeks.

### **7.5.3 Drug-Demographic Interactions**

More females experienced events of injection site reactions in the albiglutide group (12.0% females vs. 5.8% males). This trend was not observed in the all comparators of placebo groups.

There was an age-related increase in the proportion of subjects who experienced on-therapy SAEs seen in both the albiglutide group and all comparators.

### **7.5.4 Drug-Disease Interactions**

#### **RENAL DISEASE**

The proportion of subjects who experienced any AE across the renal function categories was similar in both the albiglutide and placebo group. The proportion of subjects who experienced events of nausea, vomiting and diarrhea increased as renal function decreased in the albiglutide arm. In the placebo group nausea events increased with decreased renal function. There was a trend for increased incidence of on-therapy

SAEs as renal function decreased in the albiglutide group (9.1%, 11.7%, and 14.3% for subjects with normal, mild, and moderate renal function, respectively). Similar results were observed in the placebo group.

The proportion of subjects experiencing any on-therapy AE increased as the baseline renal function decreased and this trend was similar across both the albiglutide and all comparator groups. The proportion of subjects who experienced nausea increased as renal function decreased in both groups. There was a trend for increased proportion of subjects who experienced on-therapy SAEs as renal function decreased.

### PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

The drug-disease relationship was evaluated for renally-impaired subjects in the P3-ISP by baseline renal status which included subjects with normal and mildly impaired renal function. The inclusion criteria were set at a creatinine clearance estimate threshold of >60 mL/min determined using the Cockcroft-Gault equation. However the degree of renal impairment in the Integrated Analysis of Efficacy and in the Integrated Analysis of Safety was determined using the Modification of Diet in Renal Disease (MDRD) equation described below.

$$eGFR = 186.3 \times (\text{Baseline serum creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times 1.212 \text{ (if subject was black)} \times 0.742 \text{ (if subject was female)}.$$

As a result of the MDRD calculation the applicant states that 5% to 6% of subjects were characterized as having moderate or rarely severe renal impairment. The subjects were not considered to be protocol violators as their renal impairment by the Cockcroft-Gault formula identified them as having renal function meeting the inclusion criteria.

Based on the MDRD calculation renal status was categorized as follow. :

- **Normal** renal function was defined as having  $eGFR \geq 90 \text{ mL/min/1.73 m}^2$
- **Mild** renal function was defined as having  $eGFR \geq 60 \text{ mL/min/1.73 m}^2$  to  $<90 \text{ mL/min/1.73 m}^2$ .
- **Moderate** renal function was defined as having  $eGFR \geq 30 \text{ mL/min/1.73 m}^2$  to  $<60 \text{ mL/min/1.73 m}^2$ .
- **Severe** renal function was defined as having  $eGFR <30 \text{ mL/min/1.73 m}^2$ .

### Albiglutide vs. Placebo

The proportion of subjects who experienced any AE across the renal function categories was similar in both the albiglutide placebo group as depicted in Table 85

The proportion of subjects who experienced nausea increased as renal function decreased in both the albiglutide and placebo group. Diarrhea increased as renal function decreased in the albiglutide group.

In the albiglutide group, the proportion of subjects who experienced vomiting increased as renal function decreased (2.7% of subjects with normal renal function, 4.6% for those with mild impairment, and 7.8% for those with moderate impairment). The proportion of subjects who were withdrawn due to any GI event was 1.7% for both groups. Withdrawal rates were 0.3% and 0.4%, for nausea and 0.2% and 0.0%, for vomiting in the albiglutide and placebo groups, respectively.

**Table 85: Most Common On-therapy Adverse Events Occurring in More Than 5% of Subjects and with Increasing Incidence with Decreasing eGRF (Albiglutide vs. Placebo)**

	Placebo	Albiglutide
<b>Any event (n/N [%])</b>	385/468 (82.3)	789/923 (85.5)
<b>Baseline Renal Function/Status</b>	n/N (%)	n/N (%)
Normal (eGFR ≥90 mL/min/1.73 m <sup>2</sup> )	121/149 (81.2)	246/249 (82.6)
Mild (eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> )	228/274 (83.2)	479/548 (87.4)
Moderate (eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> )	36/45 (80.0)	64/77 (83.1)
Severe (eGFR <30 mL/min/1.73 m <sup>2</sup> )		
<b>AE Preferred Term</b>		
<b>Upper respiratory tract infection</b>	n (%)	n (%)
Normal (eGFR ≥90 mL/min/1.73 m <sup>2</sup> )	9 (6.0)	37 (12.4)
Mild (eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> )	44 (16.1)	84 (15.3)
Moderate (eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> )	8 (17.8)	10 (13.0)
<b>Diarrhea</b>	n (%)	n (%)
Normal (eGFR ≥90 mL/min/1.73 m <sup>2</sup> )	14 (9.4)	36 (12.1)
Mild (eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> )	32 (11.7)	71 (13.0)
Moderate (eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> )	3 (6.7)	14 (18.2)
<b>Nausea</b>	n (%)	n (%)
Normal (eGFR ≥90 mL/min/1.73 m <sup>2</sup> )	9 (6.0)	25 (8.4)
Mild (eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> )	29 (10.6)	66 (12.0)
Moderate (eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> )	7 (15.6)	11 (14.3)
<b>Vomiting</b>		
Normal (eGFR ≥90 mL/min/1.73 m <sup>2</sup> )	7 (4.7)	8 (2.7)
Mild (eGFR ≥60 to <90 mL/min/1.73 m <sup>2</sup> )	4 (1.5)	25 (4.6)
Moderate (eGFR ≥30 to <60 mL/min/1.73 m <sup>2</sup> )	1 (2.2)	6 (7.8)

Adapted from ISS Table SP3-9.7.2 and Table 297 page 895

On-therapy SAEs by baseline renal status

PHASE 3 INTEGRATED SAFETY POPULATION (P3-ISP)

There was an increased incidence of on-therapy SAEs as renal function decreased in the albiglutide group (normal - 9.1% (27/298), mild- 11.7% (64/548) and moderate- 14.3% (11/77). Similar results were observed in the placebo group (normal -14.1% (21/149), mild 12% (133/275) and moderate -22% (10/45). (See ISS -Table SP3-16.7.2).

The most common SOC for both treatment groups was in the cardiac disorders SOC. An imbalance not in favor of albiglutide compared to placebo was observed in moderate renal impairment subgroup in the SOC of infections and infestations (3.9%, 3/77 vs.). Preferred term events for the SOC were for pneumonia (n=2), tracheobronchitis (n=1) and viral infection (n=1).

#### Albiglutide vs. All Comparators:

The overall proportion of subjects experiencing any on-therapy AE increased as baseline renal function worsened. In the albiglutide group , 80.7% (649/804) with normal renal function, 85.1% (969/1139) with mild renal impairment, and 85.5% (148/173) for those with moderate renal impairment. In all comparators 79.3% (715/902) of subjects with normal renal function, 80.9% (976/1207) for those with mild renal impairment, and 85.1% (148/174) for those with moderate renal impairment experienced an adverse event. There was 1 subject with severe impairment of renal function in the all comparators group and none in the albiglutide group

The trend for increased adverse events as renal function decreased was seen for adverse events of nausea, vomiting.

Nausea increased as renal function decreased in both groups

Albiglutide – 9.8% (79/804) of subjects with normal renal function, 11.9% (136/1139) for those with mild impairment, and 16.2% (28/173) for those with moderate impairment;

All comparators – 9.1% (82/902) of subjects with normal renal function, 11.1% (134/1207) for those with mild impairment, and 14.9% (26/174) for those with moderate impairment.

The applicant states that vomiting occurred in 4.4% and 4.9% of all study subjects in the albiglutide and all comparators groups, respectively. A review of renal impairment categories revealed similar rates of vomiting in normal renal impairment for albiglutide 3.7 % (30/804) vs. 4.0 % (36/902) in all comparators, and for mild impairment 5.4 % in albiglutide (62/1139) vs. 4.8% all comparators (58/1207).

In the moderate renal impairment group 6.9% (12/173) of albiglutide treated subjects had an AE of vomiting vs. 4% (7/174) in all comparators (ISS Table SP3-9.7.1). Overall proportions of subjects experiencing vomiting increased as renal status declined.

The proportion of subjects who were withdrawn due to any GI event was the same for both groups, with similar withdrawal rates for nausea and vomiting in the albiglutide and all comparators groups (0.5%, 0.5%, 0.4% and 0.2%, respectively)

There was an increased incidence of on-therapy SAEs as renal function decreased in the albiglutide group and all comparators groups.

There was a trend for increased incidence of on-therapy SAEs as renal function decreased in the albiglutide group (8.8% (71/804), 12.1% (138/1139), and 15.6% (27/173) (for subjects with normal, mild, and moderate renal function, respectively). Similar results were observed in the all comparators group (8.9% (80/902), 10.8% (130/1207), and 21.8% (38/174), respectively) (ISS -Table SP3-16.7.1). SAES occurring most commonly in the albiglutide and all comparators grouping for subjects with normal renal function(2 vs. 1.3%), and mild renal impairmen (1.8%, 22/1201) vs. 2.9%, 33/1139) were in the Infections and infestations SOC.

In moderate renal impairment the most commons SOC for SAES was in cardiovascular events (5.2% for each group)

#### RENAL STUDY (GLP114130)

Adverse events in both treatment groups were mild or moderate in intensity with a similar percentage of severe AEs (13.7% in the albiglutide group and 14.6% in the sitagliptin group). A total of 8 deaths (4 in the albiglutide group and 4 in the sitagliptin group) occurred during the study. See relevant sections for death (7.3.1), non-fatal serious adverse events (7.32) and adverse events of interest.

**Table 86 Overview of Adverse Events by Renal Impairment Severity (Study GLP114130 Safety Population)**

	Albiglutide (N=249)			Sitagliptin (N = 246)		
	Mild (N=128)	Moderate (N=102)	Severe (N=19)	Mild (N=128)	Moderate (N=101)	Severe (N=17)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	104 (81.3)	88 (86.3)	16 (84.2)	109 (85.2)	80 (79.2)	16 (94.1)
Any fatal AE	0	4 (3.9)	0	0	2 (2.0)	2 (11.8)
Any serious AE	10 (7.8)	22 (21.6)	0	13 (10.2)	18 (17.8)	5 (29.4)

Any related AE <sup>2</sup>	25 (19.5)	22 (21.6)	7 (36.8)	18 (14.1)	14 (13.9)	2 (11.8)
On-therapy AEs leading to withdrawal of active treatment <sup>3</sup>	6 (4.7)	17 (16.7)	3 (15.8)	4 (3.1)	15 (14.9)	7 (41.2)
Any AE by max intensity <sup>4</sup>						
Mild	50 (39.1)	32 (31.4)	5 (26.3)	51 (39.8)	31 (30.7)	3 (17.6)
Moderate	40 (31.3)	38 (37.3)	9 (47.4)	44 (34.4)	33 (32.7)	7 (41.2)
Severe	14 (10.9)	18 (17.6)	2 (10.5)	14 (10.9)	16 (15.8)	6 (35.3)
Any AE by therapy						
Pretherapy	38 (29.7)	33 (32.4)	9 (47.4)	43 (33.6)	30 (29.7)	7 (41.2)
On-therapy	98 (76.6)	87 (85.3)	15 (78.9)	104 (81.3)	78 (77.2)	16 (94.1)
Post therapy	3 (2.3)	6 (5.9)	1 (5.3)	7 (5.5)	10 (9.9)	2 (11.8)
On-therapy AE incidence rate <sup>5</sup>						

Source: Study GLP114130 Table 14.3.1-1.1.1.1, Table 14.3.1-1.6.1.1, and Listing 14.3.2-1.1.

AE = adverse event, max = maximum. 1. Note: Hypoglycemic events were excluded from this table except in serious adverse event (AE) and pretherapy AE counts. 1. Number of AEs = the total number of AEs at each level of summarization. 2. Events missing investigator-assigned relationship to study medication were considered related and included in this summary. 3. On-therapy 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. There were no pretherapy or post therapy AEs that led to withdrawal of active treatment. A subject was counted once if the subject reported 1 or more AEs. 4. A subject was counted once according to the maximum intensity experienced if the subject reported 1 or more AEs. Adverse events with a missing intensity were considered severe in this summarization. There were AEs with nonapplicable intensity; however, these events occurred in subjects with other mild, moderate, or severe events. 5. The on-therapy AE incidence rate per 100 person-years =  $100 \times (\text{number of AEs} / \text{person-years})$ , where person-years was defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the on-therapy treatment period.

*Subject with moderate and severe renal impairment had a higher incidence of GI events, hypoglycemic in events and ISRs (See appropriate subsections under Section 7.3.5).*

**Reviewer Comment: Conclusions regarding adverse events in subjects with severe renal impairment are limited by the small sample size in both the albiglutide (N=19) and sitagliptin group (N=17).**

### 7.5.5 Drug-Drug Interactions

Please see Clinical Pharmacology review for details.

### 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Neoplasms were not increased overall in albiglutide treated subjects. However, it should be noted that the duration of the clinical programs at time of the BLA submission may not have been long enough to detect malignancy potential.

### 7.6.2 Human Reproduction and Pregnancy Data

Adequate data is not available to support the use of albiglutide in pregnancy and lactation.

There were 6 pregnancies in the albiglutide group.

- 1 pregnancy was terminated early.
- 1 subject was lost to follow-up.
- 1 subject gave birth to a male who developed neonatal hyperbilirubinemia with transient tachypnea and had an abscess on the back and nape of the neck.
- 3 subjects -there were no complications reported.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of albiglutide has not been established in pediatric patients (below 18 years of age). The applicant seeks a product-specific partial waiver for albiglutide for the treatment of T2DM in children <10 years of age and is applying for a deferral for the initiation of the albiglutide pediatric studies for the in children aged 10 to <18 years.

The applicant is proposing a single study of albiglutide in pediatric patients with T2DM in the following pediatric subsets:

- Children (10-11 years)
- Adolescents (12 to <18 years)

Study design:

Randomized, double-blind, multicenter, placebo-controlled study to evaluate dose selection (Part A:PK/PD, safety and tolerability) and efficacy (Part B: glycemic parameters) of albiglutide given by SC injection in pediatric subjects aged >10 and <18 years.

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(b) (4)

(b) (4)

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

A maximum single dose of 104 mg albiglutide was administered in clinical trials without serious consequences. Data regarding overdoses in humans are not available. In the event of an overdose, appropriate supportive treatment based on clinical symptoms should be initiated. A prolonged period of observation and treatment may be necessary due to the half-life of albiglutide (5 days).

Data was not provided regarding potential for illegal use or abuse of albiglutide.

The applicant notes that due to the slow elimination of albiglutide, clinically relevant systemic concentrations may be maintained for up to 4 to 5 weeks following cessation of dosing, reducing the risk of withdrawal or rebound.

#### 7.7 Additional Submissions / Safety Issues

Study GHF112670 was conducted in subject with congestive heart failure (CHF). All safety summaries were based on all subjects randomized to treatment who had taken at least one dose of study medication.

- A total of 82 subjects were randomized, among which 30 subjects received placebo, 12 subjects received albiglutide 3.75 mg, 13 subjects received albiglutide 15 mg, and 27 subjects received albiglutide 30 mg.
- There were no deaths reported during this study.
- There were no SAEs in subjects receiving albiglutide 30mg.
  - 1 subjects had 2 events of hypotension (3.75 and 15 mg dose)
  - 1 subject had a small bowel obstruction (post surgical) and ICD device malfunction)
  - 1 subject receiving 15 mg weekly had a UTI with renal impairment and hypotension.
- No treatment emergent AEs of pneumonia, pancreatitis, retinopathy, thyroid tumors, treatment-related potential systemic allergic reactions, or hypoglycemia were reported.
- The most commonly reported AEs in the study were diarrhea, vomiting and nausea. The number of subjects with a GI event was similar in the placebo (43%) and in the 30 mg albiglutide (37%) treatment groups.
- There were no adverse event withdrawals.
- 2 events of atrial fibrillation in the albiglutide group and 1 in placebo.

Overall findings from this study did not change the safety profile as assessed from the BLA submission.

#### STUDY GLP114865 – BIOEQUIVALENCE STUDY

A transition from Process 2 to Process 3 albiglutide was conducted during the ongoing albiglutide Phase III program to confirm that there were no clinically relevant differences between Process 2 and Process 3 albiglutide with respect to safety, tolerability, immunogenicity. A dose of 30 mg of albiglutide from Process 2 and Process 3 albiglutide were administered once weekly for an additional 12 weeks beginning at Week 5 after the single-dose phase of the study was completed.

#### Safety

Overall as depicted in Table 87 there were no fatalities in the study. A greater number of subjects receiving Process 2 drug product had any adverse events (75% vs. 64%, respectively) and SAEs (3.5% vs. 1.4%). AEs leading to withdrawal were similar between groups (1.4% for both).

**Table 87: Overview of Overall Adverse Events (Study GLP114865 Safety Population)**

	Albiglutide Process 2		Albiglutide Process 3	
	n (%)	Number of AEs <sup>1</sup>	n (%)	Number of AEs <sup>1</sup>
Any AE	106 (75.2)	359	91 (64.1)	365
Any fatal AE	0	0	0	0
Any serious AE	5 (3.5)	7	2 (1.4)	2
Any related AE <sup>2</sup>	30 (21.3)	58	30 (21.1)	66
Any AE leading to withdrawal of active	2 (1.4)	2	2 (1.4)	2
Any AE by maximum intensity <sup>3</sup>				
Mild	54 (38.3)	221	49 (34.5)	219
Moderate	47 (33.3)	125	37 (26.1)	140
Severe	5 (3.5)	13	5 (3.5)	6
Any AE by therapy phase				
Pretherapy	43 (30.5)	53	38 (26.8)	67
On-therapy	100 (70.9)	303	83 (58.5)	295
Posttherapy	3 (2.1)	3	2 (1.4)	3
On-therapy AE incidence rate <sup>4</sup>	-	487.94	-	471.47

Source Data: CSR Study GLP114865 Table 14.3.1-1.1.1.

Note: Overall results include data from both the single- and multiple-dose phases.

Hypoglycemic events were excluded from this table except in serious AE and pretherapy AE counts.

1. Number of AEs = the total number of AEs at each level of summarization.

2. Events missing investigator-assigned relationship to study medication were considered related and included in this summary. Note: This row includes 3 pretherapy AEs, in 2 Process 2 subjects and 1 Process 3 subject, which were reported by the investigators as related to study medication.
3. A subject was counted once according to the maximum intensity experienced if the subject reported 1 or more AEs. Events with a missing intensity were considered severe in this summarization.
4. The on-therapy AE incidence rate per 100 person-years =  $100 * (\text{number of AEs divided by person-years})$ , where person-years was defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the on-therapy treatment period.

The incidence of any on-therapy common adverse event was higher in the Process 2 group vs. Process 3 (70.9%, 11/141 vs. 58.5%, 83/142, respectively). Preferred term events occurring with a higher incidence in Process 3 drug product vs. Process 2 product were for events of contusion (2.1% vs. 0.7%), lipase and amylase increase (2.8% vs. 0.7%, 2.8% vs. 0, respectively), nausea (9.2% vs. 7.8%) and vomiting (5.6% vs. 2.1%).

On-therapy AEs in the cardiac disorders SOC were reported for 6.4% of subjects in the Process 2 albiglutide treatment group and 2.8% of subjects in Process 3 treatment group.

The incidence of on-therapy hypoglycemia events was higher in Process 2 (7.8%, 17 events) compared to Process 3 (4.9%, 9 events). No hypoglycemia event was considered to be serious or severe and there were no hypoglycemia related withdrawals.

The proportion of subjects developing anti-albiglutide antibodies on-therapy was (0.7%, 1/141 Process 2 and 4.2% 6/142 for Process 3). There were no events of anaphylaxis or angioedema. One event was identified as a potential SAR by the SMQ strategy. Subject 1160856018, a 65-year-old female experienced a mild event of urticaria (verbatim: hives on arms/forehead) on study day 4.

The incidence of on-therapy ISRs was slightly higher for the Process 2 albiglutide group (9.2%) compared with the Process 3 albiglutide group (4.9%). The number of events reported in the Process 2 albiglutide group were also higher compared with Process 3 (23 versus 14 events).

One subject (Subject 1075856032) in the Process 3 treatment group had ALT and AST values more than 3 times the upper limit of normal during the study.

Subject 1075856032: 57-year old white female with a history of hypertension, dyslipidemia, cholelithiasis, cholecystectomy, inflammatory bowel disease (recurrent ulcerative colitis), and non-alcoholic fatty liver disease experienced mild hepatic enzyme elevations on study day 119. ALT and AST values were elevated (ALT =176 U/L; normal range, 0-48 U/L and AST = 346 U/L; normal range, 0 -42 U/L), and baseline GGT was 545 U/L (normal range, 0-45 U/L) and total bilirubin was 6.0 U/L (normal range, 0-22 U/L). Per the investigator, the subject's liver function tests (LFT) fluctuated

throughout the study. The investigator did not perform additional lab tests or imaging. The subject recovered

Three subjects in the Process 3 albiglutide group had abnormal lipase ( $>3 \times \text{ULN}$ ). These events were adjudicated by the independent blinded PAC as possible pancreatitis with a possible relationship to study drug. There were no associated GI events and LFTs were normal.

There were small and similar increases over time in mean and median amylase and lipase values in both the Process 2 and Process 3 treatment groups. There was 1 event of lipase increased in the Process 2 treatment group (lipase of  $>2 \times \text{ULN}$ ) and 4 events of lipase increased (ranging from  $>2$  to  $>5 \times \text{ULN}$ ) in 4 subjects in the Process 3 treatment group.

***Reviewer Comment: Process 2 to Process 3 switch did not demonstrate additional safety findings.***

## **8 Postmarket Experience**

Albiglutide is not currently marketed. Therefore, post-marketing data are not available.

## **9 Appendices**

### **9.1 Literature Review/References**

1. Medeiros LJ, Greiner TC. Hodgkin's disease. Cancer. 1995 Jan 1;75(1 Suppl):357-69.

### **9.2 Labeling Recommendations**

Labeling recommendations are described throughout the safety section.

### **9.3 Advisory Committee Meeting**

An Advisory Committee Meeting was not convened.

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KAVEETA P VASISHT  
11/03/2013

ALI MOHAMADI  
11/04/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology (OSE)  
Office of Pharmacovigilance and Epidemiology (OPE)**

**Epidemiology: Review of Sponsor's Proposed Study**

Date: October 2, 2013

Reviewer(s): Patricia L. Bright, M.S.P.H., Ph.D.,  
Epidemiologist,  
Division of Epidemiology 1 (DEPI 1),  
Office of Pharmacovigilance and Epidemiology (OPE),  
Office of Surveillance and Epidemiology (OSE)

Team Leader: Diane K. Wysowski, M.P.H., Ph.D.,  
Epidemiology Team Leader, DEPI 1, OPE, OSE

Acting Division Director: Solomon Iyasu, M.D., M.P.H.,  
Acting Division Director, DEPI 1, OPE, OSE

Subject: Review of the Sponsor's Proposed Study " (b) (4)  
[REDACTED]

Drug Name(s): Albiglutide for injection

Application Type/Number: BLA 125431/IND 65177

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2013-621

TSI #: Not Applicable

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/s/  
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PATRICIA L BRIGHT  
10/02/2013

DIANE K WYSOWSKI  
10/02/2013

SOLOMON IYASU  
10/02/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: 07 June 2013

To: Kaveeta Vasisht, MD, Medical Officer  
Jean-Marc Guettier, MD, Team Leader  
Mary Parks, MD, Director  
Division of Metabolic and Endocrine Products

From: Mark Avigan, MD, CM  
Associate Director, Critical Path Initiatives  
& Hepatologist  
Office of Surveillance and Epidemiology (OSE)

Through: Gerald Dal Pan, MD, MS  
Director, OSE

Drug Name: Albiglutide (GSK716155)

Dose/Formulation: 30 mg or 50 mg administered subcutaneously once per week

BLA Number: BLA125431

Applicant/sponsor: GlaxoSmithKline

Issue: Review of cases of liver injury in  
association with albiglutide

**INTRODUCTION**

In a request dated 7 Mar 2013, DMEP has asked for consultation by a hepatologist to evaluate selected cases of liver injury in association with albiglutide, a long-acting glucagon-like peptide-1 (GLP-1) mimetic agent that is being considered for approval as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

**BACKGROUND**

Albiglutide is a long-acting recombinant GLP-1 mimetic agent generated by the genetic fusion of an amino acid sequence-modified GLP-1 dimer to human albumin that is produced (b) (4). Because of its resistance to digestion by dipeptidyl peptidase (DPP) – 4, in humans albiglutide has a long circulating half-life and in clinical studies is typically administered by subcutaneous injection on a weekly or biweekly basis. GLP-1 activity linked to albiglutide and other agonists in this class of drugs pharmacologically potentiates glucose-dependent insulin secretion from pancreatic  $\beta$  cells, leading to increased hepatic glucose metabolism. GLP-1 agonists also suppress glucagon secretion, which delays gastric emptying and independently contributes to reduced blood glucose concentrations. At pharmacological concentrations, these agents can have pronounced motility effects on the upper GI tract, explaining the observation of treatment-induced nausea and/or vomiting as well as early satiety and weight loss linked to this class of compounds. Other drug-induced motility effects on gastroenterological organs are also plausible. Exenatide, another GLP-1 agonist, has also been shown to reduce cholecystokinin (CCK) - induced gallbladder emptying, compared with placebo in fasting healthy subjects. Finally, investigations to determine whether GLP-1 mimetic agents cause an increased risk for pancreatitis and/or metaplastic transformation, possibly through drug-induced changes of pancreatic ductular cells are ongoing.

In the albiglutide BLA, the sponsor has identified a number of cases of acute liver injury that occurred while study subjects were treated with the study drug. Among these cases are 6 that had ALT elevations peaking at levels greater than 5X ULN, which, based on protocol requirements, resulted in interruption or permanent discontinuation of the study drug. All of the cases improved or resolved during follow-up evaluation and none progressed to life-threatening injury. Of the 6 cases, 2 were marked by increased serum total bilirubin levels which exceeded 2X ULN. These were designated by the sponsor as serious ADRs. All of the 6 cases have been summarized in the integrated summary of safety. OSE has been consulted to evaluate the information that has been submitted surrounding these cases to determine whether albiglutide can induce clinically significant DILI. It should be noted that in the development program, the integrated safety analysis of randomized phase III trials included 2,116 study subjects treated with albiglutide - 30 mg doses vs 2,284 treated with a comparator. Another 1,416 study subjects were treated with albiglutide - 50 mg doses, using either optional or forced titration.

**Appraisal of 2 cases marked by serum ALT values  $\geq$  3X ULN and concurrent total bilirubin values  $\geq$  2X ULN**

**Case #1**

Subject # 1028179043

Investigator # 1028

Country: United States

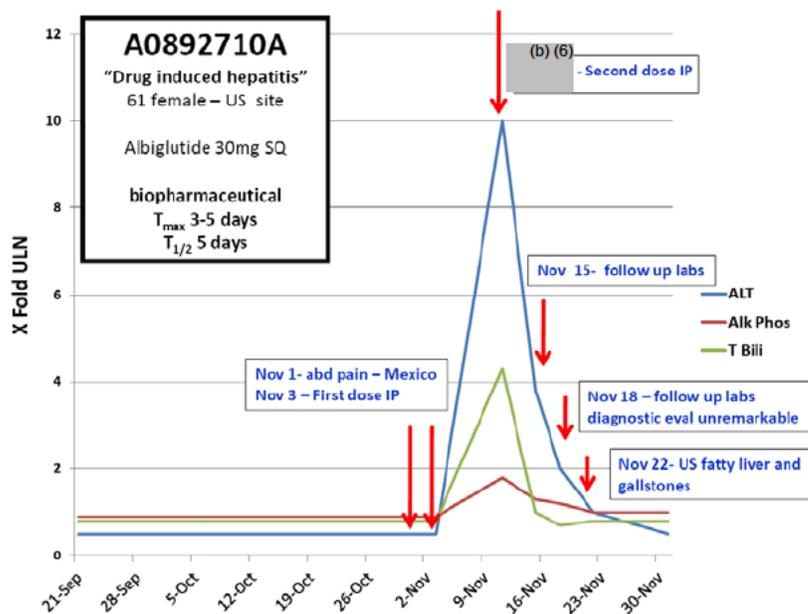
Sponsor Diagnosis of Adverse Event(s): Drug induced hepatitis

This 61-year old White female with a BMI of 36 kg/m<sup>2</sup> was enrolled in an open-label, 2 parallel-group study for the treatment of type 2 diabetes. She received the first dose of albiglutide 30 mg, on 03 Nov 2010 and a subsequent dose on (b) (6). On (b) (6) (b) (6) the same day as the second dose of albiglutide, she developed liver related lab

findings described below for which she was hospitalized and the study medication was discontinued. Neither jaundice nor other symptoms related to a systemic drug reaction were observed. There were no past liver diseases reported in her history. Concomitant medications, as reported were naproxen sodium, 220 mg, PRN, PO initiated 30 Jun 2010 for osteoarthritis, and oral metformin, 1000 mg, BID initiated 29 Apr 2009. On 01 Nov 2010, the subject saw a physician in Mexico while traveling and was given scopolamine (1 AMP, IV) for stomach pain. Upon hospitalization on (b) (6), the subject denied any new over-the-counter medications or exposures. On 22 Nov 2010, a transabdominal ultrasound with optimal imaging was performed. Imaging indicated liver hypertrophy with grade I-II fatty liver echotexture and mild fatty liver infiltrate without focal lesions. There was no ascites present. There were gallstones present. The kidney displayed evidence of inflammatory process. There were no other biliary ductal lesions or portal/hepatic vein abnormalities reported. No liver biopsy was performed. There was no reported treatment for the liver injury event. On 22 Nov 2010, the liver injury event was considered resolved. Lab data linked to this case were reported as follows:

Date	ALT U/L	AST U/L	GGT U/L	ALP U/L	T.bili mg/dl	D.bili mg/dl
21 Sep 2010	25	20	68	109	1.0	0.2
21 Oct 2010	29	24	68	102	1.1	0.1
3 Nov 2010	27	22	75	110	1.1	0.2
(b) (6)	499	511	581	226	5.6	2.5
15 Nov 2010	180	40	412	169	1.3	0.3
18 Nov 2010	94	27	--	151	0.9	--
22 Nov 2010	46	23	--	133	1.1	--
1 Dec 2010	24	15	152	115	1.0	0.2

A graphic timeline submitted by the sponsor of the ALT, ALP and T.bili measures, listed above, is shown. The red vertical arrows indicate events described in each box.



Additional studies done on 18 Nov 2010 (7 days after the peak LTs were noted): Hep B core Ab/ Hep B S Ag negative, Hep A IgM negative, HCV PCR undetectable (< 43 IU/ml), Hep E IgM negative, ANA negative, Epstein-Barr VCA IgM negative, Actin/ LKM Ab IgG negative, CPK 76 U/L (ULN 190), LDH 146 U/L (ULN=250), Lipase 26 U/L (ULN=60), and Amylase 42 U/L (ULN=103).

The event was coded by the sponsor as severe drug-induced hepatitis. The investigator concluded there was a reasonable possibility that this event of 'drug-induced hepatitis' may have been caused by albiglutide.

**Comments:**

*The reported event is consistent with an episode of acute hepatocellular injury characterized both by a rapid onset and rapid resolution. In conjunction with the predominant hepatocellular pattern marked by a 17.8 fold rise of ALT levels above baseline, there were smaller rises with respect to baseline pretreatment values of ALP (2-fold), GGT (8.5-fold) and T. bili (5.1-fold), consistent with milder cholestatic effects that accompanied the liver injury. Notably, the serum ALT, ALP and T. bili increases peaked synchronously 11 days after an unexplained episode of abdominal pain and 7 days after the first administered dose of albiglutide. All these liver test abnormalities resolved 11 days later. Moreover, the T. bili quickly reversed to 1.3 mg/dl within 4 days after the acute injury when the ALT, although decreasing, had not yet normalized (180 U/L). With the accompanying mild cholestatic changes in this case, the serial biochemical measures of liver injury are consistent with but not entirely typical of 'Hy's Law' (sentinel case of serious drug-induced acute hepatocellular injury marked by jaundice that indicates an increased likelihood for the emergence of other cases of clinically life-threatening DILI, as described in the FDA's 2009 guidance on Assessment of Pre-marketing cases of DILI). Although some drugs are known to induce hyper-acute idiosyncratic hepatocellular DILI, after just a few doses of treatment, the very rapid resolution of hyperbilirubinemia that was observed in this case is a somewhat unusual temporal signature for acute hepatocellular DILI, since the full recovery and replacement of severely drug-damaged hepatocytes, necessary to clear bilirubin normally, would typically ensue over a longer period of time.*

*In the presence of gallstones that were demonstrated by transabdominal ultrasound and in step with the initial bout of abdominal pain which prompted medical treatment with scopolamine for symptoms, another tenable etiology to consider is passage of a gallstone or biliary sludge through the common bile duct. This possible diagnosis would also be consistent with the observed rapid resolution of liver injury that was marked by a rapid normalization of both serum ALT and T. bili levels. Very transient extrahepatic biliary obstruction with or without pancreatitis often can be marked by spiking serum aminotransferase and bilirubin levels, even when only a small bump in ALP has been identified. It is noteworthy that amylase and lipase levels that were reported as normal in this case were only measured in serum drawn 7 days after the ALT and T. bili levels had peaked, at a time when these liver injury parameters had already normalized. It is*

*not inconceivable that a non-severe form of pancreatitis associated with this event may have been missed. Notably, gallstone pancreatitis has been associated in some published studies with transiently high serum ALT levels, often greater than 3XULN.*

*As albiglutide is a recombinant GLP-1 dimer albumin fusion molecule that is produced (b) (4), liver toxicity, if present, could theoretically be caused by the active moiety, an excipient, or a (b) (4) contaminant in batches of the product. Although acute hepatocellular DILI caused by albiglutide is still a possible diagnosis (Level 2 Severity; see Appendix), another diagnosis that has not been excluded is transient choledocholithiasis or biliary sludge with or without undiagnosed pancreatitis. It should be noted that exenatide, another GLP-1 agonist, has been shown to inhibit CCK-mediated gallbladder emptying. Whether there can be clinically significant GLP-1 agonist-induced effects on gallbladder motility that alter the migration of gallstones or sludge through the common bile duct in susceptible individuals, cannot be determined with currently available data.*

*Finally, a number of GLP-1 agonists have been found to be associated with a pancreatitis signal, possibly through their direct effects on pancreatic ductular cells. In the ISS database the sponsor has reported cases of albiglutide-associated and liraglutide-associated pancreatitis adjudicated as ‘possibly’ or ‘probably’ related to each of the long-acting GLP-1 agonists. Although there is no specific evidence that this case of transient liver injury was instigated by pancreatitis, it will be important to assess whether there is a causal association of albiglutide with an increased risk for pancreatic adverse events in the ongoing safety review of the BLA database.*

## **Case # 2**

Subject # 3578754988

Investigator #3578

Country: United States

A 53-year-old male in the albiglutide treatment group, had a baseline serum ALT value of 87 U/L (normal range, 0 - 48 U/L). At study entry, hepatitis B surface antigen was reported to be negative. The subject’s ALT value remained high until Week 36, and then was within the normal range until Week 78. The subject’s baseline bilirubin value was 12 µmol/L (normal range 0 to 22 µmol/L; 0.7 mg/dL, normal range 0 to 1.3 mg/dL), and remained within normal range until Week 78. At Week 78, the subjects developed acute scleral icterus, jaundice, nausea, abdominal discomfort, bloating and darkened urine. Serum ALT and bilirubin values were 2986 U/L (62.2×ULN) and 192 µmol/L (11.2 mg/dL; 8.7×ULN), respectively. At this visit, the hepatitis B surface antigen was tested and found to be positive. A diagnosis of acute hepatitis B was made and because of this SAE the subject was withdrawn from the study (544 days after first dose of study medication). The investigator assessed that the SAE was not related to study medication. At a follow-up visit 7 weeks after the onset of this event, all of the serum liver enzyme abnormalities had resolved.

**Comments:**

*The reported findings are consistent with a diagnosis of acute Type B hepatitis. With the reported acquisition of HBSAg positivity by the study subject at the time of the acute liver injury event this diagnosis is virtually certain.*

**Appraisal of 4 additional cases marked by serum ALT values  $\geq$  5X ULN**

**Case # 3**

Subject # 1200179009

Investigator # 1200

Country: United States

This 52-year old African American female with a BMI of 40 kg/m<sup>2</sup> was enrolled in a randomized, open-label, 2 parallel-group study for the treatment of type 2 diabetes mellitus.

The subject received the first subcutaneous injection of albiglutide 30 mg on 19 Oct 2010 and subsequent doses on 26 Oct 2010, 03 Nov 2010 and 09 Nov 2010 continuing weekly until 24 Nov 2010. On 24 Nov 2010, the subject experienced elevated ALT; the event occurred on the same day of the 6<sup>th</sup> dose of albiglutide administration.

Medical conditions at the time of the event included post menopausal, hypertension, first degree AV block, and dyslipidaemia. Past medical condition included Type II Diabetes Mellitus diagnosed in 2008.

**Concurrent Medical Conditions and Associated Concomitant Medications**

<b>Concurrent Medical Conditions</b>	<b>Medication, Dose, Frequency, Route</b>
Hypertension	“benazapril”, 20 mg, QD, PO (unknown date, 2009 continuing)
	nifedipine, 90 mg, BID, PO (unknown date, 2006 continuing)
Antidiabetic (Rescue only)	glimepiride, 4 mg, QD, PO (31 Jan 2011 continuing)

In addition, the subject was taking the antidiabetic medication of oral metformin at 1000 mg, BID, beginning in 2008.

**Additional Non-serious AEs Reported**

<b>Adverse Event Verbatim Term</b>	<b>Event Start Date</b>	<b>Event Stop Date</b>	<b>Outcome</b>	<b>Intensity</b>	<b>Relationship to IP</b>	<b>Con Med Dose, Frequency, Route Start and Stop date</b>
Nausea	24 Oct 2010	24 Oct 2010	Resolved	Mild	No	promethazine, 25 mg QD, PO (24 Oct 2010 to 24 Oct 2010)

On 24 Nov 2010, the subject’s serum ALT reached or exceeded protocol-defined investigational stopping criteria. There were no diagnostic imaging tests of the liver or

hepatobiliary system performed. There were no diagnostic imaging tests of the liver or hepatobiliary system performed. Liver biopsy was not performed.

The study medication was interrupted from 24 Nov 2010 to 07 Dec 2010 as a result of the event. The subject has not had a recurrence of liver function test abnormalities since resuming albiglutide. There was no treatment reported and the event was considered resolved on 09 Dec 2010.

The subject consumed alcohol on an average of 3 units (1 unit = one oz. liquor or 3 oz. wine or 8 oz. beer) per week. The subject did not report use of any herbals, complimentary or alternative medicines. There was no past liver disease medical history reported.

Multiple laboratory tests were performed, with results outlined below.

#### Laboratory Tests Results

Visit name/ Date	ALT (ULN=4 8)	AST (ULN=4 2)	GGT (ULN=4 5)	Alkaline Phosphatase (ULN=125)	Total Bilirubin (ULN=1.3)	Direct Bilirubin (ULN=0.4)
Screening 8/31/10	18 U/L	21 U/L	78 U/L	98 U/L	0.5 mg/dl	0.1 mg/dl
Wk -1 10/05/10	22	19	134	88	0.4	0.1
Baseline 10/12/10	21	23	92	89	0.4	0.1
Wk 1 10/19/10	15	17	88	100	0.5	0.1
Wk 2 10/26/10	30	41	112	116	0.7	0.1
Wk 3 11/03/10	16	20	105	109	0.5	0.1
Wk 4 11/09/10	23	24	97	101	0.5	0.1
Wk 6 11/24/10	356	77	333	132	1.0	0.3
Follow-up 12/01/10	56	24	---	105	0.3	---
Follow-up 12/07/10	24	20	---	99	0.4	---
Follow-up 01/05/11	12	16	66	97	0.4	0.1
Week 18 2/16/11	20	18	109	100	0.4	0.1
Week 26 4/13/11	15	16	64	106	0.4	0.1
Follow-up 7/22/11	14	14	52	106	0.4	0.1

Additional studies done 01 Dec 2010: Hep B core Ab/ Hep B S Ag negative, Hep A IgM negative, HCV PCR undetectable (< 50 IU/ ml), ANA negative, Epstein-Barr VCA IgM

negative, CMV IgM negative, Actin/ LKM Ab IgG negative, CPK 107 U/L (ULN 190) and LDH 159 U/L (ULN=250).

The investigator thought that there was no reasonable possibility that the event of elevated ALT may have been caused by the albiglutide.

**Comments:**

*The transient episode of acute liver injury at the time of administration of the 6<sup>th</sup> weekly dose of albiglutide is consistent with a hepatocellular pattern of injury, marked by a sudden rise of serum levels of ALT to 7.4X ULN, AST to 1.8X ULN, ALP to 1.06X ULN and T. bili to 1X ULN. It should be noted that although the latter 2 indices were not elevated with reference to population-based ULN boundaries they bumped upwards 1.5 fold and 2.5 fold, respectively, with reference to the study subject's own baseline measures. This suggests that the injury was accompanied by mild intrahepatic cholestatic changes. Although the liver injury was transient and did not recur upon reinstatement of treatment with albiglutide, drug-induced liver injury caused by this agent cannot be excluded. Studies of individuals with prior episodes of idiosyncratic DILI caused by a suspect drug have demonstrated that the recurrence rates of acute liver injury after inadvertent re-challenge are surprisingly only a few percent.*

*With regards to consideration of possible alternative causes of acute liver injury in this case, it should be noted that alcoholic hepatitis would be an unlikely explanation, given the biochemical profile of serum findings that were identified. Alcoholic hepatitis is often marked by fever, hepatomegally, and leukocytosis. Usually, with acute ethanol-induced liver injury, there are selective effects on circulating aminotransferase activities, such that AST/ALT ratios are significantly greater than 1.0. This profile is thought to be connected to a deficiency of the co-factor pyridoxine-5-phosphate. In this case, a ratio of 0.24 goes strongly in the opposite direction, consistent with other etiologies of hepatocellular damage that include viral and drug-induced liver injuries. Although common alternative diagnoses including Types A, B and C hepatitis and autoimmune hepatitis have by-and-large been excluded, certain other non-drug causes have not been excluded through lab testing or diagnostic imaging. These include Type E hepatitis and extrahepatic biliary sludge or stones (an unlikely diagnosis).*

*In summary, in the absence of known exposure to other hepatotoxic drugs, even with the negative rechallenge, a causal association of the transient liver injury with albiglutide is possible. As albiglutide is a recombinant GLP-1 dimer- albumin fusion product that is produced and (b) (4), liver toxicity, if present, could theoretically be caused by the active moiety, an excipient, or a (b) (4) contaminant in batches of the formulation.*

**Case 4**

Subject #3669754980  
Country: United States

Investigator #: 3669

This 57-year old Asian male with a BMI of 27 kg/m<sup>2</sup> was enrolled in a randomized, open-label, parallel-group study for the treatment of type 2 diabetes mellitus (diagnosed in 2008). Other than diabetes, there were no other significant medical conditions. There were no reported pre-existing liver diseases or other medical conditions.

On 06 May 2009 the baseline serum ALT was 59 U/L with other liver test results falling into a normal range (See table below; it should be noted that GGT but not ALP was monitored in this case). The subject received the first dose of open-label investigational product (weekly subcutaneous injection of albiglutide 30 mg) on 06 May 2009. The last dose of investigational product was received on 05 May 2010.

On 07 Apr 2010, 336 days after the first dose of albiglutide, the subject's serum ALT was 217 U/L and the AST was 126 U/L. On 23 Apr 2010, 352 days after the first dose of albiglutide, the ALT and AST levels rose to 369 U/L and 208 U/L, respectively; nonetheless the study drug was continued until 5 May 2010. On 16 Jun 2010, 406 days after the first dose of albiglutide and 42 days after the study drug was discontinued, the subject had an elevated ALT (241 U/L). In subsequent follow-up visits the ALT and AST levels began to slowly decrease. At the last recorded visit on 08 Sep 2010 the ALT was 93 U/L. Throughout the study the T.bili levels remained normal.

On 26 Jun 2010, a computerized tomography (CT) with optimal imaging was performed. Imaging indicated a liver of normal size with normal texture and moderate fatty infiltration. There was no ascites present. There were no hepatic lesions characterizable. There were no gallstone or gallbladder lesions present. There were no biliary ductal lesions reported. There were no portal/hepatic vein abnormalities reported. Liver biopsy was not performed.

#### Concomitant Medications

Concurrent Medical Conditions	Medication, Dose, Frequency, Route
Nutritional supplement	omega 3, 1000 mg, PRN, PO (06 May 2008 continuing)
	fish oil supplement 500 mg, BID, PO (01 May 2010 continuing)
	nature made multi vitamin 1 TAB, QD, PO (01 May 2010 continuing)

The subject was also taking the following oral antidiabetic medications: metformin 1500 mg, QD (initiated on 06 May 2008, and glyburide 1.5 mg, QD (initiated on 06 May 2008). The subject consumed an average of 1 unit of alcohol per week.

The investigator concluded that there was a reasonable possibility that the increase of serum aminotransferase levels may have been caused by the investigational product.

The results of liver-related laboratory tests that were obtained are outlined below.

### Laboratory Test Results

Date	Glycosylated Hemoglobin A1C (reference range: <6.5 TL HB) <sup>a</sup>	Alanine Amino Transferase (reference range:0-48 U/l) <sup>a</sup>	Aspartate Amino Transferase (reference range: 0-42 U/L) <sup>a</sup>	Total Bilirubin (reference range: 0.0-1.3 MG/DL) <sup>a</sup>	Gamma Glutamyl Transferase (reference range:0-65 U/L) <sup>a</sup>
06 May 2009 (Baseline)	8.1 % TL HB <sup>a</sup>	59 U/L <sup>a</sup>	34 U/L <sup>a</sup>	0.6 mg/dL <sup>a</sup>	48 U/L <sup>a</sup>
13 Jan 2010 (TP/WK36)	6.6 % TL HB <sup>a</sup>	82 U/L <sup>a</sup>	58 U/L <sup>a</sup>	0.8 mg/dL <sup>a</sup>	90 U/L <sup>a</sup>
07 Apr 2010 (TP/WK48)	7.0 % TL HB <sup>a</sup>	217 U/L <sup>a</sup>	126 U/L <sup>a</sup>	0.9 mg/dL <sup>a</sup>	118 U/L <sup>a</sup>
13 Apr 2010 (TP/WK48)		205 U/L <sup>a</sup>	98 U/L <sup>a</sup>	0.6 mg/dL <sup>a</sup>	120 U/L <sup>a</sup>
23 Apr 2010 (TP/WK48)		369 U/L <sup>a</sup>	208 U/L <sup>a</sup>	0.8 mg/dL <sup>a</sup>	128 U/L <sup>a</sup>
03 May 2010 (TP/WK48)		212 U/L <sup>a</sup>	120 U/L <sup>a</sup>	0.9 mg/dL <sup>a</sup>	103 U/L <sup>a</sup>
05 May 2010 (TP/WK52)	7.2 % TL HB <sup>a</sup>	199 U/L <sup>a</sup>	106 U/L <sup>a</sup>	0.7 mg/dL <sup>a</sup>	96 U/L <sup>a</sup>
09 Jun 2010 (Liver chemistry Follow-up)		200 U/L <sup>a</sup>	129 U/L <sup>a</sup>	0.9 mg/dL <sup>a</sup>	

Date	Glycosylated Hemoglobin A1C (reference range: <6.5 TL HB) <sup>a</sup>	Alanine Amino Transferase (reference range:0-48 U/l) <sup>a</sup>	Aspartate Amino Transferase (reference range: 0-42 U/L) <sup>a</sup>	Total Bilirubin (reference range: 0.0-1.3 MG/DL) <sup>a</sup>	Gamma Glutamyl Transferase (reference range:0-65 U/L) <sup>a</sup>
16 Jun 2010 (Liver chemistry Follow-up)		241 U/L <sup>a</sup>	142 U/L <sup>a</sup>	0.8 mg/dL <sup>a</sup>	
23 Jun 2010 (Liver chemistry Follow-up)		150 U/L <sup>a</sup>	84 U/L <sup>a</sup>	0.6 mg/dL <sup>a</sup>	
12 Jul 2010 (End of treatment)	7.4 % TL HB <sup>a</sup>	143 U/L <sup>a</sup>	88 U/L <sup>a</sup>	0.9 mg/dL <sup>a</sup>	75 U/L <sup>a</sup>
08 Sep 2010 (Follow-up)	7.0 % TL HB <sup>a</sup>	93 U/L <sup>a</sup>	51 U/L <sup>a</sup>	0.6 mg/dL <sup>a</sup>	54 U/L <sup>a</sup>

<sup>a</sup> Values are from the central laboratory.

### Comments:

*This case of asymptomatic elevations of ALT/AST during treatment with abiglutide increased to reach sustained levels (ALT range 4-7X ULN) after 36 weeks of treatment and only began to decrease gradually one month after discontinuation of the study drug at 52 weeks of continuous treatment. The study subject had a mildly elevated baseline ALT suggesting a preexisting chronic liver abnormality, possibly NASH. CT imaging revealed fatty infiltration which is consistent with but not direct proof of NASH. Since diagnostic serological studies for viral hepatitis or other systemic conditions were not*

*provided in this case, the presence of any of these processes as a background phenomenon cannot be excluded. If the injury was induced by albiglutide, the absence of increased serum bilirubin levels is consistent with criteria for DILI Level 1 severity (see Appendix) and is evidence that severe or progressing hepatocellular injury caused by exposure to the study drug did not occur. The persistence of ALT elevations for a period longer than 4 months after cessation of treatment suggests the possibility of a chronic mild hepatitic picture that could have been instigated or worsened by exposure to the drug. (In the absence of diagnostic testing, NASH as well as other non-drug etiologies were not excluded in this case). Such a prolonged course occurs in a minority of DILI cases and may take 6 months or longer to resolve, even after drug discontinuation. For some drugs that cause this form of injury, there may be a rising risk for liver fibrosis, although, usually these cases resolve and are clinically benign.*

**Case 5**

Subject # 3663753989  
Country: United States

Investigator #: 3663

This 53 year old white female with a BMI of 34 kg/m<sup>2</sup> was enrolled in a randomized, double-blind, placebo and active controlled, parallel-group study for the treatment of type 2 diabetes mellitus (diagnosed in 2007). The subject received the first dose of the investigational product (weekly subcutaneous injection of 30 mg albiglutide, daily tablets of sitagliptin placebo and daily capsules of glimepiride placebo) on 13 May 2009. The last dose of investigational product was received on 27 May 2009. On 28 May 2009, 15 days after the first dose of investigational product and one day after study medication was withdrawn, the subject experienced mild alanine aminotransferase increased which was not considered serious. There were no current or past medical history liver disease medical conditions reported. There was no diagnostic imaging performed. Liver biopsy was not performed. The subject did not report use any alcohol, herbals, complimentary or alternative medicines.

Concurrent medical conditions at the time of the event included hypertension and nephropathy. There were no past medical conditions reported. Medications administered for treatment of concurrent medical conditions are shown below.

**Concurrent Medical Conditions and Associated Concomitant Medications**

<b>Concurrent Medical Conditions</b>	<b>Medication, Dose, Frequency, Route</b>
Hypertension	lisinopril , 10 mg, BID, PO (UK Oct 2008 to 13 May 2009) losartan, 50 mg, QD, PO (13 May 2009 continuing)
Toenail fungus	terbinafine 250 mg, QD, PO (10 Apr 2009 to 17 Apr 2010)
Supplement	Vitamin D, 50000 IU, QWK, PO (Uk UNK 2008 continuing)

The subject was taking the following oral antidiabetic concomitant medications: metformin 1000 mg, BID, initiated on 08 May 2007.

All the baseline serum liver tests were normal on 13 May 2009 (see table). Results of the baseline serum testing were ALT: 34 U/L, AST: 36 U/L, GGT: 37 U/L, ALP: 89 U/L, T. bili: 0.4 mg/dl. On 28 May 2009, the subject experienced an acute transient rise in liver test results as follows: ALT: 441 U/L, AST: 222 U/L, GGT: 482 U/L,

ALP: 212 U/L, T. bili: 0.5 mg/dl. On the same day, the drug was discontinued. In the case report that was provided symptoms were not reported and the adverse event was deemed to be not serious. There was no treatment reported and the event was considered resolved on 11 Jun 2009. On that date liver test results were as follows: ALT: 32 U/L, AST: 24 U/L, GGT: Not done, ALP: 120 U/L, T.bili: 0.4 mg/dl.

**Lab test results**

Date	ALT (reference range: 0-48 U/L) <sup>a</sup>	AST (reference range: 0-42 U/L) <sup>a</sup>	GGT (reference range: 0-45 U/L) <sup>a</sup>	Alk Phos (reference range: 30-165 U/L) <sup>a</sup>	Total Bilirubin (reference range: (0-22 mg/dL) <sup>a</sup>
20 Mar 2009 Week -6	21	18	28	86	0.3
04 May 2009 Week -1	22	20	41	101	0.3
13 May 2009 Baseline	34	36	37	89	0.4
20 May 2009 Week 1	20	16	36	95	0.4
28 May 2009 Week 2	441	222	482	212	0.5
02 Jun 2009 Liver assessment	161	41	-	183	0.3
11 Jun 2009 Follow Up	32	24	-	120	0.4

<sup>a</sup> Values are from the central laboratory.

The investigator considered there was no reasonable possibility that the event was caused by the investigational product.

**Comments:**

*The transient synchronous rises in levels of serum ALT (9.1X ULN), AST (5.2X ULN), GGT (10.7X ULN) and ALP (1.2X ULN), without a bump in serum bilirubin, just two weeks after initiation of the study drug and the rapid resolution of these abnormalities are consistent with mild liver injury (Level 1 severity, see Appendix), and suggest a causal association with exposure to the active moiety, an excipient, (b) (4) contaminant in batches of the recombinant product. As in Case 1, the liver injury occurred after only a few doses of albiglutide and was characterized by a pattern of hepatocellular injury accompanied by mild cholestatic effects that were marked by respective 2.3 fold and 13 fold rises of ALP and GGT levels above baseline. The absence of a narrative description of the presence/absence of clinical symptoms surrounding this event or imaging studies to rule out gallstones or biliary sludge is diagnostically problematic. This issue is discussed more fully in Comments provided for Cases 1 and 3.*

**Case 6**  
Subject # 3599757986  
 Country: United States

Investigator # 3599

This 71-year old white male with a BMI of 29 kg/m<sup>2</sup> was enrolled in a randomized, double-blind, placebo and active controlled, parallel-group study for the treatment of type 2 diabetes mellitus (diagnosed in 2003). The subject received the first dose of investigational product (weekly subcutaneous injection of albiglutide 30 mg and daily tablets of pioglitazone placebo) on 22 Sep 2009. Masked uptitration of study drug occurred on 06 Apr 2010 within the respective study arms. For the subjects in the albiglutide arm, albiglutide was uptitrated from 30 mg to 50 mg and for subjects in the pioglitazone arm, pioglitazone was uptitrated from 30 mg to 45 mg. The last dose of investigational product was received on 21 Dec 2010.

On 21 Dec 2010, 455 days after the first dose of investigational product, the subject experienced moderate elevated alanine aminotransferase which were not considered serious.

Concurrent medical conditions at the time of the event included hypertension, nocturia, autonomic neuropathy, dyslipidaemia and gastroesophageal reflux disease. There were no past medical conditions reported. Medications administered for treatment of concurrent medical conditions are shown below.

**Concurrent Medical Conditions and Associated Concomitant Medications**

<b>Concurrent Medical Conditions</b>	<b>Medication, Dose, Frequency, Route</b>
Heartburn	omeprazole, 20 mg, QD, PO (UK UNK 2008 continuing)
Hypertension	lisinopril/hydrochlorothiazide, 20/12.5 mg, QD, PO (14 Apr 2009
Hypercholesterolemia	pravastatin, 40 mg, QD, PO (UK UNK 2008 continuing)
Vitamin supplement	multivitamin, 500 mg, QD, PO (UK Jan 2009 continuing)
	vitamin D, 800 mg, QD, PO (UK Apr 2009 continuing)

The subject was taking the following oral antidiabetic medications: metformin 1000 mg, BID initiated 14 Apr 2009, and glimepiride 4 mg, QD initiated 14 Apr 2009 and discontinued 03 Aug 2009.

On 21 Dec 2010, the subject developed transient increases of ALT (492 U/L), AST (168 U/L) and GGT (505 U/L) prompting immediate discontinuation of the study drug. Results of other serum liver tests, including ALP and T. bili were not reported. The ALT and AST abnormalities rapidly resolved within 2 weeks. There was no treatment reported and the events were considered resolved on 04 Jan 2011.

There was no current or past liver disease medical history reported. Hepatitis viral serology results were not reported. There were no diagnostic imaging tests of the liver or hepatobiliary system performed. Liver biopsy was not performed. The subject did not report use of any alcohol, herbals, complimentary or alternative medicines. The subject consumed an average of 2 units (1 unit = 1 oz. liquor or 3 oz. beer) of alcohol per week.

The investigator concluded that there was a reasonable possibility that the elevations of aminotransferases may have been caused by the investigational product.

There were no additional non-serious AEs reported. Results from laboratory tests are outlined below.

**Laboratory Results**

Date	ALT (reference range: 0-48 U/L)	AST (reference range: 0-55	GGT (reference range: 0-75 U/L)
22 Sep 2009	49	37	33
21 Sep 2010 (Week	28	30	24
21 Dec 2010 (Week	492	168	505
28 Dec 2010	71	25	247
04 Jan 2011	41	28	

Values are from the central laboratory.

**Comments:**

*A relevant clinical narrative of pertinent symptoms, clinical signs, etc., as well as a complete biochemical profile of serum liver tests associated with the reported liver injury was not provided in this case. In particular, both ALP and T. bili results were not reported. The pattern of a rapid transient rise of ALT/AST levels followed by rapid resolution of these abnormalities upon study drug discontinuation as also observed in Cases 1, 3 and 5 is in keeping with an episode of mild liver injury. Although this event occurred 455 days after initiation of treatment study-drug related causality cannot be entirely ruled out as discussed in Comments for Case 4.*

**Summary of Comments:**

*This review of six cases of liver injury associated with albiglutide in BLA125431 suggests that there is a plausible causal association of idiosyncratic episodes of mild hepatocellular injury with exposure to the GLP-1 mimetic agent which all rapidly resolved upon drug discontinuation. Some of the cases were marked by aminotransferase spikes which occurred after exposure to just a few doses of the GLP-1 agonist. Using clinical severity scoring criteria shown in the Appendix (Disease Severity Scale), with only one exception, all of the cases that may have been causally associated with albiglutide ranked as Severity level 1 cases. The single case in which a serum peak total bilirubin measure spiked to 5.6 mg/dl, only 8 days after the first dose of albiglutide, coinciding with a simultaneous spike of ALT and AST levels (ALT: 499 U/L, AST: 522 U/L) met the criteria of a Severity level 2 case, consistent with ‘Hy’s Law’. However, in this case, with the discontinuation of albiglutide, there was a pattern of rapid resolution of all the abnormal indicators. In fact, a more rapid reversal of abnormal bilirubin to virtually normal levels within 4 days after the acute injury (T. bili: 1.3 mg/dl; ALT: 180 U/L) was matched by a longer 11-day timeframe required for reversal of the ALT elevations to normal levels. This sequence of resolving parameters does not typify an expected course of serious hepatocellular DILI in which the hepatocyte recovery time required for normalizing serum bilirubin levels characteristically would be longer. Thus,*

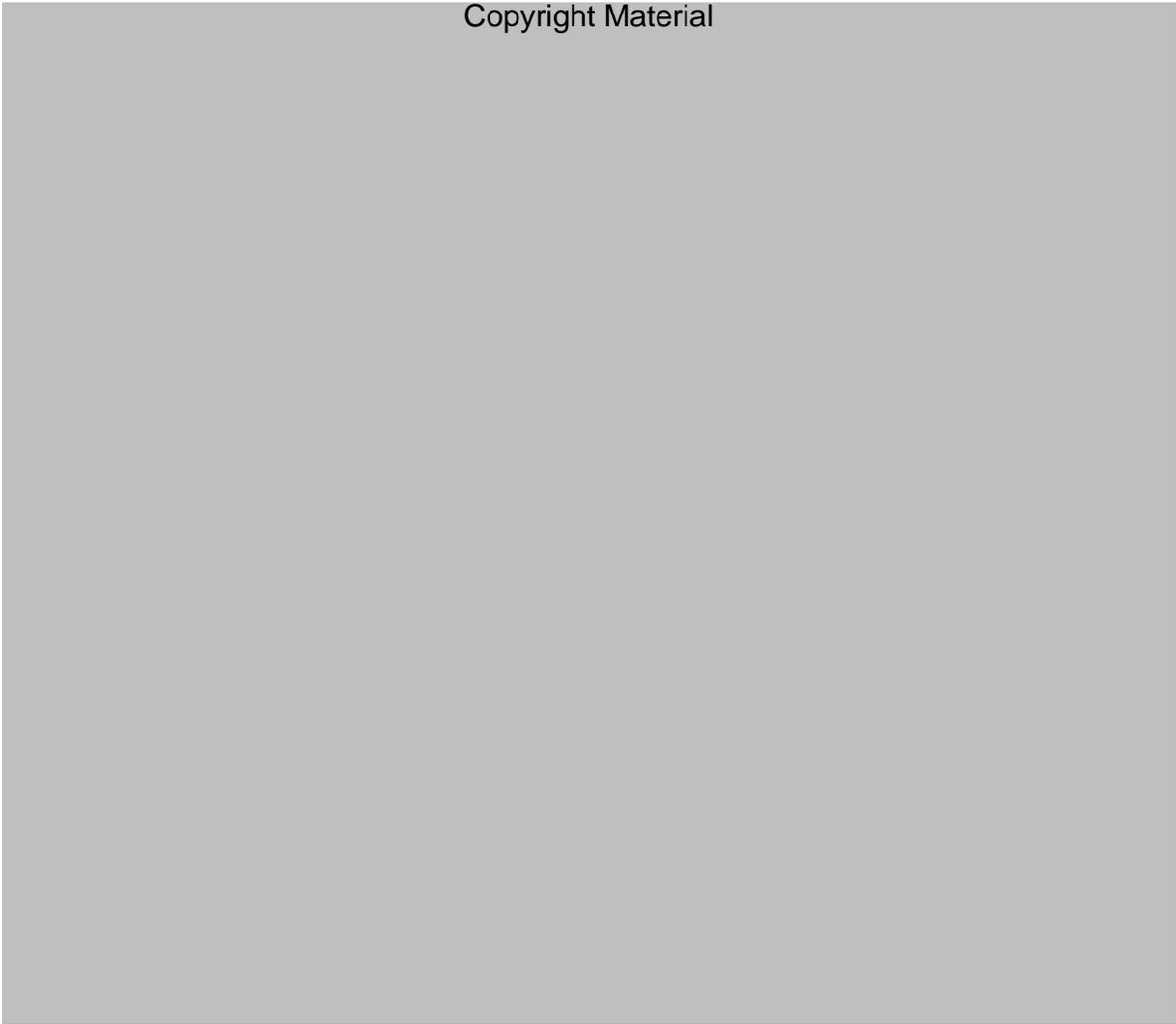
*the event may not represent a classic ‘Hy’s law’ case. With rises of GGT and slight rises of ALP in some of the cases there is the hypothetical possibility that the injuries were associated with transient cholestasis, either intra-hepatic in nature or possibly linked to reduced extrahepatic biliary flow and gallbladder motility that may be caused by some GLP-1 mimetic agents.*

*With the caveats mentioned above, if the aforementioned case does reflect acute hepatocellular injury (reversible, Level 2 severity) caused by albiglutide [identified in one study subject among the 2,116 patients who were randomized to receive this agent (30 mg doses) in the integrated Phase III studies], a risk for rare post-marketing life-threatening hepatotoxicity associated with albiglutide cannot be entirely excluded. The sponsor should be encouraged to actively follow-up and evaluate the clinical characteristics and diagnostic test results of all cases of albiglutide-associated liver injury that are reported in the future. Moreover, complete diagnostic evaluations for causality assessments will be essential.*

## Appendix

Assessment of potential drug-induced liver injury of the present cases uses the grading system for likelihood of attribution and liver disease severity developed by the National Institutes of Health's Drug-Induced Liver Injury Network (DILIN) Study Group.\*

Copyright Material



\*Fontana RJ, Seeff LB, Andrade RJ, Bjornson E, DayCP, Serrano J, Hoofnagle HJ. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology* 2010;52:73-742

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VAISHALI JARRAL  
06/07/2013

MARK I AVIGAN  
06/07/2013

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 125431**      **Applicant: GlaxoSmithKline LLC (GSK)**      **Stamp Date: 1/14/2013**

**Drug Name: Albiglutide**      **BLA Type: 351 (a)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	BLA 351 (a)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: GLP 110125 Study Title: A 16-Week, Parallel-Group, Double-Blind, Randomized, Placebo-Controlled, Multicenter, Dose-Ranging Study to Evaluate the Efficacy, Safety, and Tolerability of Multiple Doses and Multiple Treatment Regimens of GSK716155, with Byetta as an Open-Label Active Reference, in Subjects with Type 2 Diabetes Mellitus Sample Size: 361 Arms: Exenatide vs Albiglutide Location in submission: 5.3.4.2	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>EFFICACY</b>					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Studies 1- 7 Indication: Type 2 Diabetes</p> <p><b><u>Albiglutide vs. Placebo</u></b>  <b>GLP112753</b> (background of Metformin)  <b>GLP112755</b> (background of Pioglitazone +/-Metformin  <b>GLP112756</b>  <b>GLP112757</b> (background of Metformin + Glimeperide)</p> <p><b><u>Albiglutide vs. oral antidiabetic drug</u></b>  GLP112753 (background of Metformin) vs. Glimeperide vs. Sitagliptin  GLP112757 ((background of Metformin + Glimeperide) vs. Pioglitazone</p> <p><b><u>Albiglutide vs. Insulin</u></b>  <b>GLP112754</b> (Background Metformin+/- Sulfonylurea) vs. Insulin Glargine  <b>GLP 108486</b> (background Glargine + oral antidiabetic drugs) vs. Insulin Lispro</p> <p><b><u>Albiglutide vs. Liraglutide</u></b>  <b>GLP114179</b> (background oral antidiabetic drugs) vs. Liraglutide</p> <p>Pivotal Study #8 Indication: Type 2 diabetes with renal impairment</p> <p><b>GLP114130</b> (Background diet and exercise or oral antidiabetic drug) vs. sitalgiptin</p>	X			8 Phase III studies in patients with T2DM.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The primary efficacy endpoint for the individual albiglutide Phase III studies was change in HbA1c from baseline. The timing of the primary endpoint assessment ranged from

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## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					26 weeks to 104 weeks
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			Albiglutide exposure: 3122 subjects with T2DM
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			The MedDRA dictionary version 15 was used for coding AEs in the Integrated Analysis of Safety (IAS), and MedDRA dictionary version 14 was used for coding AEs in the GLP112756 clinical study report.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			CV events Thyroid Cancer Pancreatitis Hypoglycemia GI events Injection site reactions, Hepatic events Immunogenicity
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			GSK is requesting a product-specific waiver for T2DM patients aged less than 10 years and a deferral for T2DM patients aged 10 to <18 years
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			Clinical development program conducted in 19 countries. 75% of Albiglutide treatment was in the US. The sponsor notes that all clinical studies have been conducted under US regulations and ICH GCP.
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial	X			No financial

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				disclosures
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_Yes\_\_\_**

If the Application is not fileable from the clinical 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.

The application is fileable.

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Reviewing Medical Officer Date

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Clinical Team Leader Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KAVEETA P VASISHT  
03/07/2013

JEAN-MARC P GUETTIER  
03/07/2013