CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 12, 2014
From	Ali Mohamadi, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	125431
Applicant	GlaxoSmithKline
Date of Submission	January 14, 2012
PDUFA Goal Date	April 15, 2014
Proprietary Name / Established (USAN) names	Tanzeum (albiglutide)
Dosage forms / Strength	Lyophilized powder contained within single use prefilled pens administered subcutaneously as 30 or 50 mg
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
Recommended:	Approval

Reference ID: 3488113

• Introduction

Glucagon-like peptide (GLP)-1 is released from the gastrointestinal tract during meals and stimulates insulin release from the pancreatic beta-cell in a glucose-dependent manner. GLP-1 also reduces hepatic glucose production (by lowering glucagon secretion from the pancreatic alpha-cell) and slows gastric emptying. Endogenous GLP-1 has a short half-life (<2 minutes) due to rapid degradation by dipeptidyl peptidase (DPP)-4. Because patients with type 2 diabetes have reduced GLP-1 concentrations, GLP-1 receptor agonists resistant to DPP-4 degradation have been developed for the treatment of type 2 diabetes. Currently, Byetta (exenatide), Victoza (liraglutide), and Bydureon (exenatide synthetic) are the only FDA-approved GLP-1 receptor agonists. These drugs differ in their frequency of administration: Byetta is dosed twice daily, Victoza once daily, and Bydureon once weekly, all by subcutaneous route. GlaxoSmithKline has subsequently submitted a new drug application (NDA) for albiglutide (proposed tradename Tanzeum), a new GLP-1 receptor agonist to be administered once weekly by subcutaneous injection, that is the focus of this memorandum.

• Background

Albiglutide is a GLP-1 receptor agonist that acts on pancreatic beta cells to augment glucose-dependent insulin secretion. Like other currently approved GLP-1 agonists, it is a protein-based therapies that is administered via the subcutaneous (sc) route. (b) (4)

Safety concerns with GLP-1 agonists include:

- Risk of thyroid C-cell tumors, based on findings from rodent studies;
- Postmarketing reports of acute pancreatitis, including the more severe hemorrhagic or necrotizing forms with deaths;
- Worsened renal function, sometimes requiring hemodialysis, that may be attributed to dehydration due to gastrointestinal side effects;
- Increased incidence of hypoglycemia when used in combination with a sulfonylurea or insulin.

The safety and efficacy of the albiglutide product is supported in this application by eight Phase 3 trials ranging from eight months to three years in duration. These trials were designed to evaluate the safety and efficacy of two doses (30 and 50 mg) of once weekly sc injections of albiglutide among patients with type 2 diabetes mellitus (T2DM). Albiglutide was evaluated as monotherapy and as add-on to single, dual, and triple oral antidiabetic agents, and in combination with insulin glargine.

The applicant proposes labeling albiglutide for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The proposed dose is 30 mg sc once weekly, with potential to increase to 50 mg sc once weekly based on glycemic response.

As for other therapeutic agents in development for the treatment of diabetes, cardiovascular safety was a major focus of the clinical and statistical reviews for albiglutide. Another major focus of the review pertains to relatively uncommon but severe adverse reactions found in the albiglutide development program that are dissimilar to other currently approved GLP-1 agonist products, in particular: atrial fibrillation/flutter, pneumonia, and appendicitis.

- **CMC/Device**

Chemistry, manufacturing and controls data related to the drug substance manufacturing process were found to be acceptable and are detailed in the joint review authored by Drs. Joao Pedras-Vasconcelos, Arulvathani Arudchandran, and Montserrat Puig. Dr. Pedras-Vasconcelos also performed the immunogenicity review and did not find any deficiencies.

Albiglutide (GSK716155/TANZEUM™) is a 73 kDa recombinant human glucagon-like peptide 1 (GLP-1)-human serum albumin (HSA) fusion protein produced through (b) (4) of a genetically modified strain of *Saccharomyces cerevisiae*. The cells (b) (4) Albiglutide (b) (4) to produce bulk drug substance (DS).

Albiglutide consists of two consecutive (b) (4) fused copies of a 30 amino acid sequence of recombinant GLP-1 fragment 7-36 genetically linked to (b) (4) of recombinant human serum albumin (HSA). Each rGLP-1 sequence has an Ala-Gln substitution at position 8 to increase the drug half-life by conferring resistance to DPP-IV mediated proteolysis. The predicted MW based on the amino acid sequence is 72971.4 Da. (b) (4)

Manufacturing process

The albiglutide DS manufacturing process included 3 distinct phases, each associated with a specific manufacturing site and process scale. These have been designated, and for the remainder of this review will be referred as, **Process 1**, **Process 2**, and **Process 3**. (b) (4)

(b) (4)

In summary:

(b) (4)

Table 1: Comparison of Key CMC Findings Between Process 1 and Process 2 Albiglutide Drug Substances

(b) (4)

Note: n.d. = not detected
Source: CMC review

As shown in Table 1, (b) (4)

(b) (4)

The second major difference was the (b) (4)

Table 2: Comparison of Key CMC Findings Between (b) (4) Albiglutide Drug Substances

(b) (4)

Source: CMC review

Several differences were seen in (b) (4) when compared to (b) (4) These differences are highlighted in yellow in the table. (b) (4)

These changes appear to have led to no significant pre-clinical or clinical impact (pK/pD or immunogenicity).

Drug Substance/Product Purity

During the review cycle, the CMC team conveyed concerns to the applicant regarding monitoring of DS and DP purity using its [redacted] (b) (4) The applicant's method did not include acceptance criteria for minor peaks other than [redacted] (b) (4) which CMC believes does not provide adequate monitoring of purity, as minor peaks can vary up to 2% and unexpected impurities would be allowed. While not an approvability issue, during the review cycle FDA recommended that the applicant develop, validate, and implement an ultra-performance liquid chromatography (UPLC) analytical method to better assess purity of albiglutide DS and DP. GSK began initial assay development in late 2013 but ran into technical difficulties with method robustness with [redacted] (b) (4) With development still ongoing, development of a viable UPLC method has been proposed as a post-marketing commitment (PMC).

Drug Release and Stability

Binding of HSA to the FcRN *in vivo* results in recirculation of HSA, similar to antibodies that also bind to the FcRN. This recirculation helps HSA and antibodies avoid degradation and increases their serum half-life, and Dr. Pedras-Vasconcelos postulates in his review that the pharmacokinetics (PK) of albiglutide may be controlled in part by FcRN-driven recirculation. At the request of the Agency, the applicant developed a Biacore-based assay to characterize the binding of the HSA portion of albiglutide to FcRN. However, validation reports were never submitted, and in communications with the CMC team, the applicant argued that their assay was not meant to be as sensitive as other physio-chemical methods they used to ascertain release and stability characteristics of the HSA portion of the molecule. At the request of the Agency, on June 4, 2013 the applicant submitted details regarding its FcRN binding assay method and a qualification report, and it stated its intentions to begin full validation of the assay at that time. CMC considered this response to be adequate, and as a PMC has requested that the applicant continue to develop, validate, and implement an FcRN binding assay to monitor functionality of the HSA portion of the DS and DP for release and stability.

• Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology and toxicology data were found to support approval of BLA 125431 and are detailed in Dr. Ronald Wange's review.

In summary, the safety of albiglutide was supported by an acute subcutaneous and intravenous study in the mouse and repeat subcutaneous dose studies for durations of up to 15 days in the mouse and 52 weeks in the monkey. Acute toxicity associated with single high doses of albiglutide was assessed in mice at doses of 50, 200, 500 and 1000 mg/kg SC and 500 mg/kg IV. A transient, dose-dependent body weight drop (11-15%) was seen in both sexes at SC doses >200 mg/kg and the 500 mg/kg IV dose. Microscopic findings were observed in male reproductive tissues: epididymis

(vacuolation and cell debris), seminal vesicle (vacuolation), and prostate (vacuolation and lymphocyte infiltration) of male mice at 500 mg/kg IV and in the epididymis (vacuolation and cell debris) at doses > 500 mg/kg SC. The maximum tolerated dose in this study is considered to be >1000 mg/kg SC and >500 mg/kg IV. Based on the microscopic findings in male reproductive tissue, the male NOAEL is 200 mg/kg SC (240X the MRHD) and <500 mg/kg IV. The female NOAEL is 1000 mg/kg SC (1200x the MRHD) and 500 mg/kg IV.

For the repeat-dose general toxicity studies, Dr. Wange's review focused on the monkey studies, as the interpretation of the 15-day rodent study was confounded by a significant anti-drug antibody (ADA) response, which will be discussed below. In general, the results of the monkey toxicology studies were consistent with known agonist response at the GLP-1 receptor: decreased food consumption, emesis, dehydration and decreased body weight gain (and occasionally transient frank body weight loss). These effects were most marked following the first few doses and became attenuated thereafter. Transient reductions in blood glucose were also seen following the first dose in the 4-week monkey toxicity study. In the pivotal 52-week toxicity study, no dose-limiting toxicity was seen at doses up to 50 mg/kg/week (the highest dose tested). There were mild injection site reactions (minimal perivascular mononuclear cell infiltrates) in albiglutide-treated animals. Most notably, albiglutide (and exenatide used as a comparator) caused a dose-related increase in pancreas weight; however, there were no histopathologic abnormalities detected in the pancreases of albiglutide-treated monkeys, and stereological examination suggested that all components of the pancreas exhibited a proportional increase in volume. It is unknown whether the increase in pancreas weight is reversible, as there was no recovery group in the 52-week study, and pancreas weight was not determined in any of the shorter duration toxicity studies. There were no albiglutide-related findings in the thyroid. The NOAEL for the 52-week monkey study was 50 mg/kg/week (75X the maximum anticipated clinical exposure), the highest dose tested.

As per Dr. Wange's review, albiglutide was found to be highly immunogenic in animals. In mice, the ADA response caused diminished exposure to albiglutide and was associated with type 3 hypersensitivity reactions in a subset of animals. Therefore, it was concluded that longer-term studies (exceeding ~2 weeks) with albiglutide in rodents would likely be uninformative to clinical risk. As a result, some of the development and reproductive toxicology studies were subdivided into multiple 2-week exposure periods. In addition, it was not feasible to conduct chronic toxicity or 2-year carcinogenicity studies in rodents. While albiglutide was also immunogenic in monkeys, the ADA response did not appreciably alter exposure to active drug in the majority of monkeys, nor did it discernably contribute to the toxicity findings of the monkey studies.

In reproductive and developmental toxicity studies in mice, prolonged estrous cycle, embryofetal lethality, and bent/wavy ribs in the fetus were observed at 50 mg/kg/day (39X the maximum anticipated clinical exposure), a dose that caused signs of maternal toxicity (body weight loss, reduced food consumption, and reduced plasma glucose). In a mouse male fertility study at doses up to 50 mg/kg/day (34X the maximum anticipated clinical exposure), there were no effects on male reproductive performance, male reproductive organs, or embryonic survival. In mouse pre/postnatal development studies, albiglutide produced dose-dependent reduced postnatal body weights of F1 pups, generally at all doses. Possibly as a consequence of reduced body weights,

there were slight dose-dependent delays in the onset of sexual maturation in both sexes. At doses up to 50 mg/kg/day there were no adverse effects on maternal pregnancy, parturition, lactation, or offspring survival. Also, there was no effect on neurobehavioral or reproductive function or survival or growth of the offspring. Exposure to albiglutide from Day 15 post-coitus to Day 10 post-partum resulted in a dose-related decrease in the live litter size for the second filial generation, likely related to a reduction in the number of implantation sites in pregnant females.

Mortalities occurred only during lactation and have not been observed in previous toxicology studies in non-pregnant, non-lactating, or pregnant mice. The findings and timing of onset were consistent with lactational ileus, and mortality was reduced by taking measures to reduce metabolic demand (culling litter size) and adding high energy dietary supplements. Dr. Wange does not consider the propensity of albiglutide to cause/exacerbate lactational ileus in mice to be clinically relevant, since the relative stress of lactation energy demands is much lower in humans and humans have relatively large energy reserves, compared to mice.

- **Clinical Pharmacology/Biopharmaceutics**

The clinical pharmacology team recommends approval of the NDA. For complete details, please refer to the review authored by Dr. Ritesh Jain; a summary of his review follows.

The clinical pharmacology program for albiglutide included 10 Phase 1 studies to investigate its pharmacokinetics (PK) and pharmacodynamics (PD) in both healthy volunteers and subjects with T2DM. These included:

- Single and repeat dose PK/PD studies;
- A PD study to evaluate the impact of albiglutide on gastric emptying of both solids and liquids;
- A relative bioavailability study of single doses of albiglutide administered subcutaneously to 1 of 3 different sites (arm, leg or abdomen);
- Drug interaction studies;
- A tQT safety study; and
- A PK study in subjects with varying degrees of renal function

The PK of albiglutide in T2DM subjects was studied following single dose administration of 30 mg. The absorption half-life of albiglutide following sc injection is approximately 1.5 days. Following sc administration, albiglutide has a prolonged terminal half-life of approximately 5 days and steady-state exposures are achieved after 4 to 5 weeks of once-weekly administration. Following sc administration of a single 30 mg dose to patients with T2DM, maximum concentrations were reached 3 to 5 days post dose with mean peak albiglutide concentration (Cmax) of 1.74 µg/mL and mean area under the time-concentration curve of 465 µg•hr/mL. Similar exposure is achieved with sc administration of albiglutide in the abdomen, thigh, or upper arm. Following a single dose administration of albiglutide 30 mg in T2DM subjects, the mean estimate of apparent volume of distribution (V/F) was 11 L. As albiglutide is an albumin fusion molecule, plasma protein binding was not evaluated.

In this application, only one Phase 3 trial (GLP112756) provided information regarding the dose-response relationship of albiglutide. In this study, patients were randomized to either receive albiglutide 30 mg without up titration or to receive albiglutide 30 mg followed by up titration to 50 mg at week 12 (forced titration). Since GLP112756 had a forced titration design, there were three analyses directed at dose response in the study by the applicant. First, the overall data was compared between dosing arms. Second, because many events in the 50 mg arm occurred while subjects were still taking 30 mg (i.e., first 12 weeks), an analysis comparing the pre- and post-titration period in the 50 mg arm was performed. Finally, the treatment arms were compared in the post-titration period (Weeks 12-52).

According to Dr. Jain's review, in study GLP112756 there was evidence of a dose-response relationship for mean change from baseline in HbA1c in T2DM patients, with a larger decline in HbA1c with increase in dose to 50 mg weekly compared to 30 mg

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weekly. In terms of adverse events, there was an increase in the proportion of patients with injection site reactions, sinusitis and pain in extremity with dose. The density of these adverse events (AEs) also increased with increasing dose. However for these AEs the density is lower in the post-titration phase compared to the pre-titration phase. Thus, Dr. Jain has concluded that no clear dose-response relationship for adverse events could be identified in study GLP112756.

Based on population PK analysis including a Phase 3 trial in patients with mild, moderate and severe renal impairment, exposures of albiglutide were increased by approximately 30 to 40% in severe renal impairment compared to those observed in type 2 diabetic patients with normal renal function. Dr. Jain does not recommend a dose adjustment in patients with renal impairment, which is supported by a dedicated safety and efficacy Phase 3 study in patients with mild, moderate, and severe renally-impaired patients. However, there is limited long term clinical experience in patients with severe renal impairment (only 19 subjects in the Phase 3 program), and these patients experienced a relatively higher frequency of gastrointestinal events in the Phase 3 trial. No formal studies of albiglutide were performed in patients with hepatic impairment. Analysis of the population PK data revealed that neither gender, race, nor body weight had a clinically relevant effect on the pharmacokinetics of albiglutide.

There was a significant increase in the gastric emptying time (t½) for both solid and liquid meals, following a single 100 mg sc dose of albiglutide (with the 100 mg dose chosen to mimic probable steady-state concentrations). For solid meals, the gastric emptying t½ increased from 1.14 hours at baseline to 2.23 hours following albiglutide dosing. For liquids, gastric emptying t½ increased from 0.28 hours at baseline to 0.69 hours following albiglutide dosing.

Despite the increase in gastric emptying time following single dose administration, no clinically relevant drug-drug interaction was seen following multiple dose administration of albiglutide on the pharmacokinetics of warfarin, digoxin, simvastatin or oral contraceptives. Co-administration of albiglutide with simvastatin resulted in an approximately 2-fold increase in peak plasma concentrations of the active metabolite, simvastatin acid. The clinical pharmacology team has proposed that providers use caution when prescribing albiglutide in patients who are on simvastatin dose of 20 mg or greater.

Of note, all Phase 3 studies used drug substance manufactured using Process 2, whereas the proposed commercial formulation utilizes drug substance manufactured using Process 3. Therefore, to bridge the drug substance manufactured through Process 2 to Process 3, the applicant conducted a single dose bioequivalence study, as well as a 12 week multiple dose safety and tolerability study utilizing the drug substances from Process 2 and Process 3. Dr. Jain's analysis demonstrated that there was no statistically significant difference in the AUC and Cmax of albiglutide between Process 2 and Process 3, and the two products were bioequivalent after a single sc dose of 30 mg. The 90% confidence intervals of the ratios of the t square means for area under the time-concentration curve and Cmax were within the criterion interval of 0.80 to 1.25.

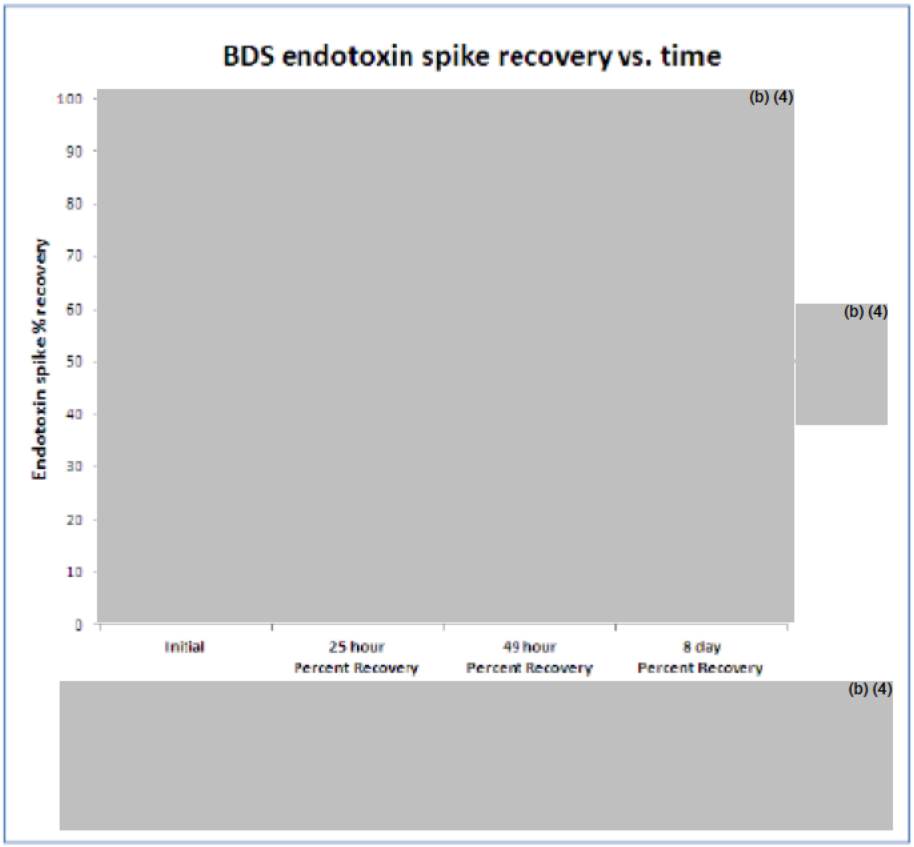
- **Clinical Microbiology**

Following adequate resolution of items described in Dr. Bo Chi and Dr. Lakshmi Narasimhan's reviews and summarized below, the clinical microbiology team has recommended approval of the NDA. For complete details, please refer to the CMC micro reviews.

The drug product is [redacted] (b) (4) It is supplied in a clear glass dual chamber cartridge (DCC) with the [redacted] (b) (4) lyophilized albiglutide cake in the front chamber and [redacted] (b) (4) diluent in the rear chamber. The DCC is assembled into a pen injector, which is comprised of a clear plastic cartridge holder and opaque plastic pen mechanics. The pen injector is designed to deliver an injection volume of 0.5 mL after reconstitution of the lyophilized drug product (30 mg or 50 mg).

Upon initial review, the microbiologists voiced a number of concerns regarding the applicant's endotoxin testing plan and initial results. Please see Dr. Chi's review for complete details. In brief, the agency raised concerns regarding the applicant's endotoxin recovery results and the [redacted] (b) (4), which did not include endotoxin control in a series of communications with the applicant between April and June, 2013. The applicant submitted two responses, one on April 26, 2013, followed by another on June 14, 2013. Upon review of the applicant's responses, and as noted in Dr. Chi's review, CMC-Micro had continued questions regarding 1) the applicant's proposed endotoxin assay, which was concerning both for the presence of sample matrix interference at lower dilutions and a questionable Limit of Quantification of the assay (the proposed test method was capable of detecting endotoxin levels [redacted] (b) (4) whereas the established acceptance criterion is [redacted] (b) (4) and 2) low endotoxin recovery for both drug substance and drug product, which were possibly due to the use of [redacted] (b) (4) during the recovery studies (see Figure 1 below, which shows that in [redacted] (b) (4) recovery was [redacted] (b) (4)

Figure 1: Albiglutide Drug Substance Endotoxin Recovery From [redacted] (b) (4)



These issues were communicated to the applicant both in information requests and during the Mid Cycle Review Meeting on June 26, 2013, and in order to fully address the CMC-Micro concerns, the applicant submitted a major amendment to its application on July 12, 2013, extending the review clock by three months.

In its July 12, 2013 amendment, the applicant committed to add (b) (6), re-qualifying the assay to determine the lowest excipient solution dilution and to rule out sample (drug product) interference. The limit of detection for the test was (b) (4) and the applicant proposed to change (b) (6) the excipient solution to (b) (4) In a subsequent response on November 8, 2013, the applicant agreed to perform an endotoxin recovery using (b) (4) to help determine the reliability of the test results. The results are summarized in Tables 3 and 4 below:

Table 3: Summary of Endotoxin Recovery Results for Excipient Solution in (b) (4)

Container Material	Sample Number	Tempe-rature (°C)	Time Point	Endotoxin Result (EU/mL)	Percent Recovery (T_x / T_0 x 100)	Result (Pass/Fail)
[redacted] (b) (4)						

When [redacted] (b) (4) were used, endotoxin recovery [redacted] (b) (4) acceptance criterion for [redacted] (b) (4)

Table 4: Summary of Endotoxin Recovery Results for Excipient Solution in [redacted] (b) (4)

Container Material	Sample Number	Time Point	Endotoxin Result (EU/mL)	Percent Recovery (T_x / T_0 x 100)	Result (Pass/Fail)
(b) (4)					

The excipient solution in (b) (4) Endotoxin recovery decreases more significantly at the earlier time points.

To summarize, LER was observed for excipient solution and bulk drug product solution under all conditions. LER was observed for DCC when testing was performed outside the normal testing window. LER was also observed in the initial time point results based on the theoretical spiking endotoxin concentration, although the turbidimetric-kinetic method was successfully validated to a product dilution of (b) (4) according to EP, USP and JP.

The LER effect has been observed and recently reported for (b) (4), both excipients present in the albiglutide excipient solution, bulk drug product solution and drug product. Albiglutide is a fusion protein containing the human

serum albumin (HSA) moiety, which is also known to inhibit endotoxin detection in the LAL assay. In her review, Dr. Chi has noted that despite the continued concerns with low endotoxin recovery, because of these known effects and because the microbial and endotoxin control of the albiglutide manufacturing process is generally acceptable, the risk of introducing endotoxin to the DP process is relatively small. Furthermore, she points out that the drug substance release test result is generally reliable if the bulk is (b) (4) (b) (4) Therefore, it is the CMC-micro recommendation that, while these issues should not preclude approval of albiglutide, postmarketing studies should be conducted to understand the mechanism for low endotoxin recovery for the albiglutide DS and DP, including confirming the pyrogenicity of the LER samples in rabbits. In addition, as a post-market commitment, a reliable endotoxin test should be developed and validated for DP in-process and release samples.

- **Clinical/Statistical- Efficacy**

This section will focus on the efficacy results from the eight controlled Phase 3 trials. Please also see Dr. Japobrata Choudhury's statistical review and Dr. Kaveeta Vasisht's clinical efficacy review for further details.

Table 5 below summarizes the pivotal Phase 3 albiglutide trials.

Table 5: 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]
On-going studies							
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 [1]	MET (immediate/ extended release) ≥1500 mg daily or MTD [1] <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 [1]	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 / ex-tended 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]

			daily				
Monotherapy							
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 [2]	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]
Completed Studies							
Add on to insulin glargine							
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 [3] + 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-parallel group	T2DM, inadequate glycemic control on current background therapy MET, TZDs, or SUs or any combination	MET, SU [4] and TZD either alone or in combination	1. Albiglutide (30 mg weekly with uptitration to 50 mg weekly at Week 6) 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)	1:1 Albiglutide [422/346] Liraglutide [419/340]	Change from baseline HbA1c to week 32	None
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 controlled on diet /exercise or background therapy of MET, TZDs, or SUs or any combination	Diet & Exercise or MET, TZD and SU [4] 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 ISE
[1] 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.
[2] 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.
[3] 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 alphaglucosidase inhibitors, with the exception of sulfonylureas, glinides, or dipeptidyl peptidase-IV inhibitors which were discontinued).
[4] 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.

As shown above, the Phase 3 pivotal trials were analyzed individually by both the applicant and the review teams for efficacy. These studies were randomized, multicenter, and placebo and/or active controlled studies. In the placebo-controlled trials, which ranged in duration from 52-104 weeks, blinding was maintained for albiglutide by having non-albiglutide-treated patients inject with placebo. In studies versus active comparators, the treatment duration ranged from 26-104 weeks. Two albiglutide doses (30 and 50mg) were evaluated across the Phase 3 program; all studies started with a dose of 30mg once weekly, with six allowing for optional

uptitration to 50mg, and two requiring uptitration to 50mg at either six or 12 weeks following study initiation. Study medication was administered subcutaneously into the abdomen, alternating right and left sides of the body.

The Phase 3 trials had similar inclusion and exclusion criteria. Entry criteria included age ≤80 years (except for study GLP108486, with an upper age limit of 75 years) and type 2 diabetes with inadequate glycemic control (defined as baseline HbA1c 7- 10%, except for Study GLP108486, baseline 7-10.5%). Exclusion criteria for all trials included ALT and/or AST ≥2.5x ULN, total bilirubin >1.5x ULN, and family history of medullary thyroid cancer. Other exclusion criteria included history of significant cardiovascular disease, such as myocardial infarction, within the 2 months prior to screening or Class III or IV New York Heart Association heart failure. The applicant prespecified fasting plasma glucose cutpoints (e.g., fasting plasma glucose >250 mg/dL at Week 12 in some trials) that would trigger the need for glycemic rescue therapy. Patients meeting these criteria were discontinued from the Phase 3 trials.

The primary efficacy endpoint of the Phase 3 trials was change in HbA1c from baseline to the primary assessment time points (26, 32 or 104 weeks). Secondary endpoints included change from baseline in HbA1c over time, change from baseline in fasting plasma glucose (FPG), proportion of subjects who achieved an HbA1c treatment goal of <6.5% or <7.0%, time to hyperglycemia rescue and change from baseline in body weight. HbA1c was measured by Ion Exchange High Performance Liquid Chromatography (HPLC) for all samples tested in the Phase 3 efficacy studies.

As discussed by Dr. Choudhury, 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 one dose of study medication, had a baseline assessment and at least one post-baseline assessment (scheduled or unscheduled) for the primary endpoint of HbA1c. 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 myocardial infarction (yes versus no), and age category (<65 years versus ≥65 years), with baseline HbA1c as a continuous covariate. The applicant used a prespecified margin of 0.4% for all non-inferiority comparisons, with the exception of study GLP108486 (open-label, add-on to insulin glargine study), which had a margin of 0.3%.

Secondary efficacy variables, including fasting plasma glucose and body weight, were analyzed using the same ANCOVA model used for the primary efficacy variable.

Demographics

Drs. Vasisht and Choudhury discuss patient demographics in detail in their reviews. Briefly, 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/m2. 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 % 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 Asian subjects and a smaller proportion of White subjects compared to the other studies. In addition, a greater proportion of subjects had lower mean BMI (<25 kg/m2) compared to other studies.

Baseline HbA1c ranged from 7.85 to 8.48% in the Phase 3 studies. The mean HbA1c for albiglutide treated subjects was 8.22%. The majority of subjects had HbA1c <8% (45.5%) and had diabetes duration of <10 years; mean duration of diabetes among albiglutide treated subjects was 8.11 years (range 4-13 years). There were relatively few subjects aged 75 or older, and 14.5% were between 65 to 75 years of age. Renal impairment was observed in 62.0% of subjects across treatment groups.

Efficacy Results

Primary Efficacy Endpoint: HbA1c

Table 6 below summarizes the changes in HbA1c from baseline to the primary endpoint for all pivotal Phase 3 studies, with brief written summaries of each individual study to follow.

Table 6: Summary of changes in HbA1c from baseline to the primary endpoint (ITT- LOCF)

Study # Endpoint (Weeks)	Treatment Arm	N[1]	Baseline HbA1c (%) Mean (SD)	LS Mean Change (SE)[2]	LS Mean Difference (95% CI) Albiglutide – Comparator (or placebo)[2]	P value
Monotherapy						
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
Add on to Metformin						
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
Add on to Pioglitazone +/- Metformin						
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
Add on to metformin and sulfonylurea						
GLP112757	Albiglutide	265	8.18 (0.908)	-0.55 (-0.65,-0.44)		
52 weeks	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 (0.16,0.49)	-0.87 (-1.07, -0.68)	S: <0.0001
Add on to insulin glargine						
GLP 108486 26 weeks	Albiglutide	279	8.47 (0.924)	-0.82 (0.058)		
	Lispro	278	8.43 (0.858)	-0.66 (0.058)	-0.16 (-0.32, 0.00)	NI: <0.0001 S: 0.0533
Compared to insulin glargine +/- metformin (with or without sulfonylurea)						
GLP112754 52 weeks	Albiglutide	493	8.28 (0.9)	-0.67 (0.044)		
	Lantus	238	8.36 (0.954)	-0.79 (0.064)	0.11 (-0.04, 0.27)	NI: 0.0086 S: 0.1463
Compared to liraglutide						
GLP114179 32 weeks	Albiglutide	398	8.18 (0.892)	-0.78 (0.047)		
	liraglutide	402	8.15 (0.841)	-.99 (0.046)	0.21 (0.08, 0.34)	NI: 0.0846

Compared to sitagliptin in renally impaired subjects						
GLP114130 26	Albiglutide	242	8.08 (0.858)	-0.83 (0.062)		
	Sitagliptin	236	8.22 (0.908)	-0.52 (0.063)	-0.32 (-0.49, -0.15)	NI: <0.0001 S: 0.0003

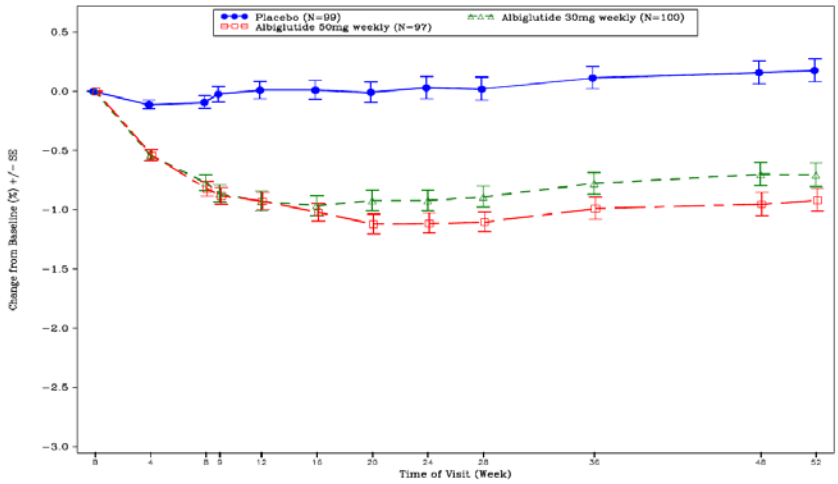
Source Clinical Study Report (CSR): CSR GLP112756 Table 13, page 80, CSR GLP 112753 Table 17, page 90, CSR GLP 112755 Table 13 page 80, CSR GLP112757 Table 13 page 92, CSR GLP108486 Table 18 page 74 , CSR GLP112754 Table 17 page 93, CSR GLP114179 Table 14 page 65, CSR GLP114130 Table 14 page 94.
1. Number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

Results of Individual Phase 3 Studies

Monotherapy: Study GLP112756

This 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 primary analysis compared superiority of albiglutide 50mg versus placebo followed by superiority testing of albiglutide 30 mg compared to placebo. Mean baseline HbA1c values were similar across treatment groups. Reductions in HbA1c values from baseline to the primary endpoint were observed for both the 30 mg and 50 mg albiglutide treatment arms, with adjusted mean reductions of -0.7% and -0.89% occurred with the 30 mg and 50 mg doses, respectively. Conversely, an increase in HbA1c was observed in the placebo group. 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 2.

Figure 2: Change from baseline HbA1c through week 52 ITT LOCF



CSR GLP112765 Figure 3 page 81

Add on to metformin: Study GLP112753

This study compared albiglutide to placebo and active comparators sitagliptin and glimepiride added on to background metformin theapy. The primary analysis was a superiority analysis of albiglutide versus placebo followed by non-inferiority testing

comparing albiglutide to the active comparators at week 104. A decrease in HbA1c from baseline to the primary endpoint was observed in the albiglutide, sitagliptin and glimepiride treatment groups. Model adjusted mean change in HbA1c 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 GLP112755

The primary objective of this study was to evaluate the efficacy of albiglutide administered in combination with pioglitazone (+/- metformin) as compared to placebo in combination with pioglitazone (+/- metformin) on HbA1c change from baseline to week 52. A reduction in HbA1c from baseline to Week 52 was observed in both the albiglutide treatment group and placebo. The model-adjusted mean change in HbA1c 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 to -0.56%) was statistically significant (p<0.0001).

Add on to metformin and sulfonylurea GLP112757

This 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

In GLP12757, 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.

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.

In GLP 108486, a decrease in mean HbA1c 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 (± SU). A multiple comparisons adjustment strategy was implemented. The first test evaluated the primary efficacy analysis of HbA1c 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.

In GLP112754, a decrease in HbA1c from baseline to week 52 was observed in both the albiglutide and the insulin glargine treatment groups. The adjusted LS mean change in HbA1c 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).

Compared to liraglutide: Study GLP114179

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 HbA1c 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 HbA1c from baseline occurred in both arms of GLP114179, -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).

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.

In GLP 11413, the model-adjusted LS mean change in HbA1c 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).

Secondary Efficacy Endpoints

Fasting Plasma Glucose

See Table 7 below for data regarding FPG in the Phase 3 trials. In the monotherapy study (GLP112756), albiglutide demonstrated a statistically significant reduction in FPG for both the 30 mg and 50 mg dose levels compared to placebo (-34 and -42.8 mg/dL,

p<0.0001 for both). 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 7: Summary of changes in Fasting Plasma Glucose (FPG) from baseline to the primary endpoint (ITT- LOCF)

Study # Endpoint (Weeks)	Treatment Arm	N[1]	Baseline FPG mg/dl Mean (SD)	LS Mean Change (SE)[2]	LS Mean Difference (95% CI) Albiglutide – Comparator (or placebo))[2]	P value
Monotherapy						
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
Add on to Metformin						
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
Add on to Pioglitazone +/- Metformin						
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
Add on to metformin and sulfonylurea						
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
Add on to insulin glargine						
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
Compared to insulin glargine +/- metformin (with or without sulfonylurea)						
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
Compared to liraglutide						
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
Compared to sitagliptin in renally impaired subjects						
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.

Body Weight

See Table 8 below for data regarding body weight in the Phase 3 trials. 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 compared with albiglutide. 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 8: Summary of changes in Body Weight (Kg) from baseline to the primary endpoint (ITT- LOCF)

Study	Treatment arm	N[1]	Baseline Body weight (kg)	LS Mean (SE)[2]	LS Mean Difference (95% CI)[3]	P value
Monotherapy						
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
Add on to Metformin						
GLP112753	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
Add on to Pioglitazone +/- Metformin						
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
Add on to metformin and sulfonylurea						
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
Add on to insulin glargine						
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
Compared to insulin glargine +/- metformin (with or without sulfonylurea)						
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

Compared to liraglutide						
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
Compared to sitagliptin in renally impaired subjects						
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.

Other Endpoints

As seen in Table 9, a higher proportion of subjects on albiglutide met HbA1c levels < 7% when compared to placebo.

Table 8: Proportion of patients with HbA1c <7% (ITT- LOCF)

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

Conclusions

- **Safety**

Dr. Vasisht conducted the primary clinical safety review for albiglutide. This section of the memorandum will focus on potential safety signals identified by Dr. Vasisht and adverse events of interest, including findings related to cardiovascular safety, thyroid cancer, liver safety, hypoglycemia, gastrointestinal events (including pancreatitis), immunogenicity, injection site reactions, and diabetic retinopathy.

The safety dataset consisted of all randomized patients who received at least one dose of albiglutide). The number of subjects and duration of exposure was greatest in the Phase 3 trials, and these trials contributed the largest share of safety data in the NDA. For purposes of this review, the safety analysis will include patients from the seven integrated Phase 3 studies Phase 3 Integrated Safety Population, P3-ISP), not including the renal study (to be discussed separately).

In total, 4,400 subjects participated in the seven integrated Phase 3 trials. 2,116 were exposed to albiglutide compared with 2,284 exposed to placebo or active comparators. Exposure for Phase 3 studies by treatment group and dose using NDA submission cutoff data cutoff dates is shown in Tables 28 and 29 of Dr. Vasisht's review. Approximately 123, 677, 297 and 885 individuals were exposed to albiglutide for 26, 52, 104 and 156 weeks, respectively.

The integrated safety analyses were based on pooled data from all randomly assigned subjects who received at least one dose of study treatment in the seven Phase 3 studies. Safety population subjects were analyzed according to the treatment received. The applicant evaluated the safety of albiglutide by comparing patients in the treatment arms with all comparators, placebo comparators only, or active comparators only. Of the seven Phase 3 studies included in the safety analysis, two were placebo controlled (GLP112755, GLP112756), three were active controlled (GLP114179, GLP108486, GLP112754), and two had both active controls and placebo (GLP112753, GLP112757).

The 4-Month Safety Update (4MSU) included pooled data from five ongoing Phase 3 studies. This update had a data cutoff date of December 24, 2013 and included controlled extension data from the five ongoing trials. As of this data cutoff date two of seven trials had completed parent and extension phases (i.e., GLP114179 and GLP108486).

Patient Disposition
As discussed by Dr. Vasisht, a minimum of 95.6% of randomly assigned subjects received at least one dose of study drug (Safety Population). Subject disposition by treatment group is detailed in Table 9 below:

Table 9: Subject Disposition by Treatment Group (Phase 3-ISP)

	Albiglutide vs. All		Albiglutide vs. Placebo[2]		Albiglutide vs. Active Comparators[3]	
	All Comparators	Albiglutide	Placebo	Albiglutide	Active Comparators	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)
Reason for Discontinuing Active Treatment						
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[4]	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.

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). Reasons for discontinuation among albiglutide-treated patients included adverse events (3.1% - 10.3%), protocol violations (0.3% - 2.3%), noncompliance with the study protocol (1.1% - 4.1%), loss to follow-up (1.6% - 6.8%), and withdrawal of consent (2.6% - 17.8%). The ITT population represented at least 94.4% of the randomized population in each study.

Deaths

As discussed by Dr. Vasisht, there were a total of 42 treatment-emergent deaths in the clinical program (including the 120-day safety update database), with 20 occurring on albiglutide and 22 occurring on comparator. The overall incidence of deaths was balanced between albiglutide and comparator arms, with the highest proportion of deaths for both groups occurring in the neoplasms SOC (6 patients, 0.3% among albiglutide-treated patients compared with 9 patients, 0.4% among all comparators). The majority of neoplasm-related deaths in both arms were single preferred term events, with the exception of lung cancers: in all comparators, there were four lung cancer-related deaths, compared with two among albiglutide-treated patients.

Dr. Vasisht has provided narratives for all deaths in her clinical review, and in summary, I concur with her assessment that there is no concerning signal for death with albiglutide, although event rates are low.

Serious Adverse Events

Dr. Vasisht reviewed all serious adverse events (SAEs) occurring in completed albiglutide trials included in the NDA submission. The overall incidence of serious adverse events was numerically similar in the albiglutide (224 events,10.6%) and comparator groups (235 events, 10.3%). Dr. Vasisht notes that in particular, pneumonia, atrial fibrillation, asthma, appendicitis, myocardial infarction, and transient ischemic events occurred at a somewhat greater numerical incidence among albiglutide-treated patients than among comparators. Table 10 below highlights all

SAEs with a greater numerical incidence among albigutide-treated patients than comparators, with greater than two cases noted. Pancreatitis, major cardiovascular events, and thyroid cancer are discussed further under Adverse Events of Interest.

Table 10: Serious adverse events identified by Dr. Vasisht with >2 cases and a greater numerical incidence among albiglutide-treated patients than comparators

System Organ Class	All Comparators (N=2284) n	%	Albiglutide (N=2116) n	%
	235	**10.3**	**224**	**10.6**
Infections and infestations				
Pneumonia (including lobar)	3	0.2	12	0.5
Appendicitis (including perforated)	0		5	0.2
Cardiac disorders				
Atrial fibrillation	2	0.1	9	0.4
Myocardial infarction	3	0.1	5	0.2
Arteriosclerosis coronary artery	0		3	0.1
Gastrointestinal disorders				
Gastritis	0		3	0.1
Pancreatitis	1	0	3	0.1
Nervous system disorders				
Transient ischemic attack	3	0.1	7	0.3
Cerebrovascular accident	3	0.1	6	0.3
Migraine	1	0	3	0.1
General Disorders				
Non-cardiac chest pain	4	0.2	5	0.2
Vascular disorders				
Deep vein thrombosis	1	0	3	0.1
Respiratory, thoracic and mediastinal disorders				
Asthma	1	0	4	0.2
Pulmonary embolism	1	0	3	0.1

Modified from ISS Table SP3-19.1.1, Page 10447.

Because of concerns in animal studies, which have been outlined by Dr. Wange in his

Pharmacology/Toxicology review, Dr. Vasisht's review contains narratives and an assessment of the serious events that may be immune-related. Upon evaluation of the narratives, I concur with Dr. Vasisht's assessment that the serious immune system events were either exacerbations of pre-existing conditions, not clearly immune-mediated, or lacked adequate information to assign causality.

In her review, Dr. Vasisht has paid particular attention to imbalances among SAEs not favoring albiglutide for pneumonia, appendicitis, and atrial fibrillation, none of which are labelled in the adverse reactions or warnings/precautions sections for the other approved GLP-1 agonists. These SAEs will be given added attention here.

Appendicitis Events

At the time of NDA submission, there were 4 cases of appendicitis and 1 case of perforated appendicitis in albiglutide-treated subjects (5/2116, 0.2%) compared with none among all comparators. All of these cases were considered SAEs by the investigator. There was one additional case of uncomplicated appendicitis among albiglutide-treated patients submitted with the 4MSU (none among comparators). The majority of appendicitis events occurred in females ranging from 40-70 years of age.

After reviewing the narratives for all patients with appendicitis in the albiglutide Phase 3 studies, I agree with Dr. Vasisht that there does not appear to be a clear-cut mechanistic link between albiglutide and the development of appendicitis. Nonetheless, the overall numeric imbalance is noteworthy, and given that this is an adverse event with a potentially serious outcome, it does warrant inclusion in the label as an adverse reaction.

Pneumonia

Albiglutide has been shown to bind to the FcRn receptor, a major histocompatibility complex class I-like molecule that functions to protect IgG and albumin from catabolism. To date, a relationship between receptor binding and pneumonia events has not been elucidated. This section will cover all pneumonia events categorized as SAEs; non-serious pneumonia events are discussed later in this review.

As a whole, 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 11, SAEs among albiglutide -reated subjects included 13 cases of pneumonia (0.6% of subjects) compared to 3 cases of pneumonia in all comparators (0.1%).

Table 11: Serious Events in the Lower Respiratory Tract Infection (P3-ISP All Comparator Grouping)

	All Comparators (N=2284)		Albiglutide (N=2116)	
HLT Preferred Term	N (%)	# events/ AE Density	N (%)	# events/ AE Density
Lower respiratory tract And lung infections	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

A review of the narratives indicates that all subjects experiencing serious events of pneumonia were hospitalized. Among albiglutide-treated patients, 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. The 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. 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 sufficient information regarding relevant risk factors.

When considering additional cases submitted with the 4MSU, 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 her review, Dr. Vasisht concurs with the applicant’s assessment that the higher incidence of respiratory events in the albiglutide group supports a conclusion inclusion of pneumonia in the proposed product labeling as an adverse reaction.

Atrial Fibrillation (AF)

At the time of NDA submission, while overall events in the cardiac disorders SOC were balanced (49/2116, 2.3% from albiglutide vs. 48/2284, 2.1% in all comparators), there was an imbalance for SAEs of atrial fibrillation (9/2116, 0.4% for albiglutide vs. 2/2284, 0.1% in all comparators). Atrial flutter events occurred in 2 subjects in the albiglutide groups and none of the subjects in the all comparators group. In the 4MSU, there was one additional case of atrial fibrillation reported in the albiglutide group, and none among comparators.

In her review, Dr. Vashisht has provided narratives for the nine albiglutide-treated patients who developed SAEs for atrial fibrillation, as well as for two additional cases of atrial flutter that were considered SAEs by the applicant. I have reviewed these cases and included them below:

- 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.

- Subject 3716754986: 77-year old male developed **atrial fibrillation** 660 days after the first dose of albiglutide. He was diagnosed with hyperthyroidism (although TSH was noted to be 4.63 IU/L).

- 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.

- 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

- 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.

- 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 hemi block 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.

- 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 reaction (>90) described as redness and itching. No action was taken for study medication.

While many subjects experiencing serious on-therapy events of atrial fibrillation and flutter had a history of arrhythmia or other contributory risk factors that may confound an assessment of study drug causality, it is clear that there is an imbalance not in favor of albiglutide for SAEs related to atrial fibrillation and flutter. The applicant has identified these arrhythmia events as an important identified risk and proposed labeling atrial fibrillation/flutter as adverse reactions. However, given the severity of these conditions, consideration should be given to raising atrial fibrillation/flutter to the "Warnings and Precautions" section of the label.

Withdrawals Due to Adverse Events

Dr. Vasisht has reviewed the adverse events associated with patient withdrawal pooled across all completed clinical trials included in the NDA submission. She notes that withdrawals due to adverse events occurred in 7.8% of all albiglutide-treated patients and in 5.7% of comparator treated patients, with this difference driven by withdrawals due to injection site reactions, (2.1% vs. 0.6%, respectively). Injection site reactions are discussed below under Adverse Events of Interest.

Dr. Vashist notes that there were slightly higher rates of withdrawals in the albiglutide arm versus comparators in the system organ class (SOC) for infections (0.3% versus 0.1%, respectively) and skin disorders (0.3% versus 0.2%). These were primarily single events, and I agree with her assessment that the 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, although in many cases there was an overall lack of information to determine the cause for withdrawal.

Table 12 summarizes the most common adverse events associated with patient withdrawal in the Phase 3 trials. Injection site reaction was the the only adverse events associated with patient withdrawal that occurred in >1% of the pooled albiglutide-treated patients.

Table 12: 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 (P3-ISP)

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)
General disorders and administration site conditions	13 (0.6)	44 (2.1)
Injection site reaction	0	31 (1.5)
Injection site rash	0	4 (0.2)
Gastrointestinal disorders	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)
Investigations	13 (0.6)	14 (0.7)
Alanine aminotransferase increased	0	4 (0.2)
Cardiac disorders	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.

Treatment Emergent Adverse Events

Dr. Vasisht has summarized treatment-emergent adverse events occurring across all completed albigultide trials included in the NDA submission. Table 13, adapted from Dr. Vasisht's review, shows adverse events occurring in >2% of the pooled albigutide-treated patients and occurring with an incidence >0.2% higher in the pooled albiglutide group than in the pooled placebo group.

Table 13: On-therapy Adverse Events Overall – Albiglutide versus All Comparators, Occurring in More Than 2% of Subjects in Either Treatment Group (P3-ISP

Proffered Term	All Comparators N=2284	Number of AEs/Density1	Albiglutide	Number of AEs/Density1
	2284		2116	
Any event	1840(80.6%)	10076/227.6	1766(83.5%)	11042/327.69
Upper respiratory tract infection	**256 (11.2)**	**337 / 9.29**	**274 (12.9)**	**345 / 10.24**
Diarrhea	**209 (9.2)**	**273 / 7.52**	**272 (12.9)**	**374 / 11.10**
Nausea	**242 (10.6)**	**283 / 7.80**	**243 (11.5)**	**351 / 10.42**
Nasopharyngitis	**209 (9.2)**	**273 / 7.52**	**190 (9.0)**	**248 / 7.36**
Injection site reaction	**45 (2.0)**	**142 / 3.91**	**187 (8.8)**	**1171 / 34.75**
Urinary tract infection	**187 (8.2)**	**254 / 7.00**	**156 (7.4)**	**196 / 5.82**
Headache	**181 (7.9)**	**228 / 6.28**	**156 (7.4)**	**190 / 5.64**
Hypertension	**165 (7.2)**	**180 / 4.96**	**156 (7.4)**	**166 / 4.93**
Sinusitis	**111 (4.9)**	**145 / 4.00**	**130 (6.1)**	**157 / 4.66**
Back pain	**140 (6.1)**	**160 / 4.41**	**125 (5.9)**	**133 / 3.95**
Bronchitis	**147 (6.4)**	**173 / 4.77**	**123 (5.8)**	**144 / 4.27**
Arthralgia	**135 (5.9)**	**161 / 4.44**	**122 (5.8)**	**154 / 4.57**
Cough	**134 (5.9)**	**162 / 4.46**	**115 (5.4)**	**132 / 3.92**
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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Several of the adverse events occurring more frequently with albiglutide in this analysis are consistent with the pharmacologic mechanism of action of the drug (e.g., nausea, vomiting) and appear dose-related. Constipation, diarrhea, and fatigue were also increased with albiglutide and also appear dose-related. An association with albiglutide for some of the other adverse effects is more questionable.

As previously discussed, pneumonia and atrial fibrillation were adverse reactions found to have a higher incidence of SAEs in albiglutide-treated patients than among comparators. When taking into account both SAEs and non-serious AEs combined, both atrial fibrillation (and atrial flutter) and pneumonia are still more common in

albiglutide-treated patients and will be discussed further below.

Atrial fibrillation/flutter

Cumulative data reveal an imbalance in on-therapy events of atrial fibrillation/flutter in the P3-ISP, occurring in 1.3% (27/2116) of subjects in the albiglutide treatment group compared to 0.6% (14.2284) in all comparators. As previously described, many events were serious, with an imbalance not in favor of albiglutide.

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 and have previously been discussed in this review.

Table 14: Summary of Adverse Events in the Preferred Terms of Atrial Fibrillation and Atrial Flutter (P3-ISP, data at week 104)

SAEs Preferred Term					
Atrial fibrillation	2(0.1%)	3/0.08	9 (0.4%)	9/0.27	3.91(0.78- 9.59)
Atrial flutter	0	0	2 (0.1%)	2/0.06	NA
Preferred Term	**Placebo N=468**		**Albiglutide N=923**		**RR (95% CI)**
	n (%)	**No. AEs/density**	**n (%)**	**No. AEs/density**	
Atrial fibrillation	3 (0.6%)	3/0.36	7 (0.8%)	8/0.45	1.31 (0.34-
Atrial flutter	0	0	1 (0.1%)	1/0.06	NA
SAEs Preferred Term					
Atrial fibrillation	0	0	0	0	
Atrial flutter	0	0	0	0	
Overall Total AEs Preferred Term	**All comparator N=2284**		**Albiglutide N=2116**		**RR (95% CI)**
	n (%)	**No. AEs/density**	**n (%)**	**No. AEs/density**	
Atrial fibrillation	11 (0.48%)	12/0.33	22 (1.0%)	24/0.71	1.77 (0.82-
Atrial flutter	0	0	5 (0.2%)	6/0.18	NA

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. Eighteen out of 25 subjects did not have a history of arrhythmias, however in 12 of those subjects, Dr. Vasisht notes that the arrhythmia event occurred with another concurrent adverse event that may have been contributory. Dose dependency for atrial fibrillation/flutter events was not observed: of the 30 events in albiglutide subjects, 14 occurred at the 30 mg dose and 16 at the 50 mg dose.

Overall, men were more likely to have an event of atrial fibrillation/flutter in both arms (17/25, 68% for albiglutide-treated subjects vs. 8/11, 73% in comparators). The mean age for subjects developing an on-therapy arrhythmia in the albiglutide group was 66 years (mean age of subjects in the P3-ISP was 55 years). The majority of subjects (84%) had mild/moderate renal impairment, and in addition 32% (8/25) of albiglutide treated subjects and 46% (5/11) of all comparators had a prior medical history of arrhythmia.

Of note, many of the atrial arrhythmia events (12/30 events) in the albiglutide program occurred in study GLP112754 (albiglutide vs. insulin glargine). In this study, 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.

Pneumonia:
A higher proportion of subjects treated with albiglutide developed on therapy (serious and non-serious) events of pneumonia (17/923), 1.8% vs. placebo 3/468, 0.6%. The overall incidence of on-therapy pneumonia was higher in the albiglutide group compared to all comparators (37/2116, 1.8% vs. 18/2284, 0.8%, respectively. There was also a slightly higher proportion of lobar and primary atypical pneumonia in the albiglutide arm vs. all comparators.

Table 15: P3-ISP: Non-Serious and Serious Events in the Lower Respiratory Tract Infection

	All Comparators (N=2284)		Albiglutide (N=2116)		
HLT Preferred Term	n (%)	Number of events/ AE density[1]	n (%)	Number of events/ AE density[1]	RR (95% CI)
Lower respiratory tract and lung infections	176 (7.7%)	221/ 6.1	166 (7.9%)	202/ 6.0	1.01 (0.81, 1.25)
Bronchitis	147 (6.4%)	173/ 4.8	123 (5.8%)	144/ 4.2	0.87 (0.68, 1.12)
Pneumonia	18 (0.8%)	19/ 0.5	37 (1.8%)	37/ 1.1	2.28 (1.25, 4.19)
Lower respiratory tract infection	18 (0.8%)	26/ 0.7	12 (0.6%)	14/ 0.4	0.90 (0.41, 1.94)
Lobar pneumonia	1 (0.0%)	1/ 0.3	3 (0.1%)	3/ 0.1	2.80 (0.18, 44.37)
Bronchopneumonia	2 (0.1%)	2	2 (0.1%)	2/ 0.1	1.17 (0.10, 13.67)
Pneumonia primary atypical	0	0	2 (0.1%)	2	NA

	Placebo (n=468)		Albiglutide (n=923)		
HLT Preferred Term	n (%)	Number of events/ AE density	n (%)	Number of events/ AE density	RR (95% CI)
Lower respiratory tract and lung infections	43 (9.12)	55/ 6.54	75 (8.1%)	90/ 0.87	0.87 (0.60, 1.25)
Bronchitis	35 (7.5%)	43/ 5.11	55 (6.0%)	64/ 0.78	0.78 (0.51, 1.89)
Pneumonia	3 (0.6%)	3/ 0.36	17 (1.8%)	17/ 0.95	2.62 (0.81, 8.45)
Lower respiratory tract infection	7 (1.5%)	8/ 0.95	7 (0.8%)	9/ 0.50	0.47 (0.16, 1.31)
Lobar pneumonia	1 (0.2%)	1/ 0.12	0	0	0

1. Density = no. of AEs per 100 patient years
ISS Table 212 and 213 page 630 -631. 1. Density = no. of AEs per 100 patient years

Dose Dependency for Adverse Events

Dose response-related AEs were primarily assessed in study GLP112756

(monotherapy trial). 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). Overall on-therapy events were similar between placebo, albiglutide 30 mg and albiglutide 50 mg (81. 2 vs. 84.2 vs. 86.9%, respectively).

Overall, the proportion of subjects reporting on-therapy AEs through Week 104 was 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: sinusitis, urinary tract infection, gastroesophageal reflux disease, injection site reaction and extremity pain. The greatest imbalance between doses occurred for preferred term events of injection site reaction (2% among placebo versus 9.9% for albiglutide 30mg and 18.2% for 50 mg).

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 injection site reactions (3% versus 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). Evaluation of the post-uptitration period alone demonstrated that a higher proportion of subjects in the 50 mg arm (12.5%) compared to those who stayed on 30 mg (8.2%) had an event of injection site reaction. However, the event density was lower in the 50 mg arm (31.95/100 patient years versus 42.25/100 patient years for 30 mg).

Adverse Events of Interest

Major Adverse Cardiovascular Events

Please see Dr. Vasisht's safety review and Dr. Bo Li's biometrics review for detailed evaluations of the applicant's pre-marketing evaluation of cardiovascular safety in the albiglutide clinical development program.

As previously discussed, the Division has requested that applicants of new pharmaceuticals for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. The 2008 guidance on this topic asks applicants to do the following during the planning stage of their drug development programs for therapies for type 2 diabetes:

- Establish an independent cardiovascular endpoints committee to prospectively and blindly adjudicate major cardiovascular events during phase 2 and 3 clinical trials.
- Ensure that the phase 2 and 3 clinical trials are appropriately designed so that a prespecified meta-analysis of major cardiovascular events can reliably be performed.
- Enroll patients at increased cardiovascular risk, such as elderly patients and those with renal impairment.

The guidance states that, to support approvability from a cardiovascular standpoint, the applicant should compare the incidence of major adverse cardiovascular events (MACE) with the investigational agent to the incidence of MACE occurring with the control group and show that the upper bound of the two-sided 95 percent confidence

interval for the estimated risk ratio or hazard ratio is less than 1.8 with a reassuring point estimate. If this upper bound is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally will be needed to definitively show that this upper bound is less than 1.3. If the premarketing data show that this upper bound is less than 1.3 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally may not be necessary.

In the albiglutide program, 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.

The applicant conducted a meta-analysis of the cardiovascular events that occurred in 9 Phase 2b/3 trials in albiglutide clinical program (Studies GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP108486, GLP114130, GLP114179 and GLP110932). This meta-analysis was the first of a two-part group sequential testing strategy. Using this strategy, if the first formal meta-analysis of the primary composite endpoint was found to have an upper-bound less than 1.8 at a one-sided alpha-level of 0.01225 (corresponding to a 97.55% CI), the product would meet the CV guidelines outlined in the FDA guidance.

The agreed upon primary endpoint was major adverse cardiovascular event (defined here as MACE+), a composite endpoint consisting of the following adjudicated events: cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina. All CV events were adjudicated by an independent, blinded clinical endpoint committee (CEC), according to a prespecified adjudication plan. The comparator group was comprised of subjects taking either a placebo or an active control (sitagliptin, glimepiride, pioglitazone, liraglutide and insulin). 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.

As described in Dr. Li's review (and shown in Table 16 below), among the 5,107 subjects in the CV safety analysis population, 44 of 2,524 albiglutide subjects had at least one adjudicated MACE+ event, while 47 of 2,583 comparator subjects experienced the primary endpoint events. The incidence rate of MACE+ was 10.4 per 1,000 patient-years in the pooled albiglutide group, as compared to 10.6 per 1,000 patient-years in the pooled all comparator group. The estimated hazard ratio of albiglutide compared to all comparator was 0.93 with a 97.55% CI of (0.55, 1.58) for MACE+. This meets the FDA requirements for filing and approval.

Table 16: Primary Analysis Results for MACE+ (CVE, on-study)

		Albiglutide (*N* = 2524) [PY = 4214.7]	Comparator (*N* = 2583) [PY = 4448.2]
MACE+ Endpoint			
	Events [IR*]	44 [10.4]	47 [10.6]
	HR (97.55% CI)†	**0.93 (0.55, 1.58)**	

*: Per 1,000 PY. †: Cox proportional hazards model stratified by trial

Using the strict definition of MACE, a total of 82 subjects experienced at least one adjudicated MACE event, with 40 subjects reporting an event in the pooled albiglutide group and 42 subjects reporting an event in the pooled all comparator group. The estimated hazard ratio of albiglutide compared to all comparators was 0.97 with a 97.55% CI of (0.55, 1.69) for strict MACE. The Mantel-Haenszel (M-H) risk ratio and risk difference results are consistent with the primary analysis result based on the hazard ratio. Sensitivity analyses were also conducted to investigate the impact of imbalanced number of pending adjudication between the two comparison arms. The results are consistent with the result of primary analysis.

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 M-H risk ratio (M-H RR) was 1.07 with 97.55% CI (0.69, 1.65).

The difference between albiglutide and all comparators in developing a CV related event as measured by MACE+ was also evaluated in subgroups by age, gender, race, region, baseline risk factors and duration of treatment. Dr. Li's analysis of the data did not indicate any concerns specific to these subgroups.

In addition to the above approaches, several sensitivity/supportive analyses were conducted that explored strict MACE endpoint, incorporated different effect measures (risk difference and risk ratio), and examined various censoring schemes, secondary comparisons and subgroup analyses. While various scenarios resulted in different values of the effect estimates, these results are consistent with the primary finding.

<u>Thyroid-Related Events</u>

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. 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.

As detailed in Table 17, 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 comparator 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. Not included in this table, one case of medullary thyroid cancer was identified in an albiglutide-treted patient post-therapy.

Table 17: P3-ISP -On therapy Thyroid Adverse Events Identified by MedDRA Query with at least one event in the albiglutide group (Albiglutide versus All Comparators)

System Organ Class SOC	Placebo N=468	Albiglutide N=923
	n (%)	n (%)
Any Event	8 (1.7)	19 (2.1)
Endocrine disorders		
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#	0	1(0.1)
Hyperthyroidism	1(0.2)	1(0.1)
Neoplasms*		
Any Event	3 (0.6)	4(0.4)
Thyroid neoplasm	2 (0.4)	4(0.4)
Thyroid cancer	1(0.2)	1(0.1)
Investigations		
Any Event	1(0.2)	3 (0.3)
Increased blood calcitonin	1 (0.2)	3 (0.3)
Metabolism and Nutrition		
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 p
# Sec. = Secondary hyperparathyroidism.

Thyroid Cancer

The applicant 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).

- Forty unique subjects with anatomic thyroid abnormalities were identified and are described in Table 18 below. 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-treated subject, 1 placebo subject, and 2 active comparator subjects). There were 3 cases of papillary thyroid carcinoma (1 albiglutide-treated subject vs. 2 all comparators) and 1 cases of medullary thyroid cancer (1 placebo subject).
- One 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 18.

Table 18: P3- ISP Description of anatomic thyroid abnormalities

	All Comparators 2284	Albiglutide 2116
# of subjects with nodules or potential nodules	21	19
Confirmed thyroid cancer	3	2
Confirmed non – malignant neoplasm	2	0
Others	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).

Calcitonin

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 are believed to stimulate calcitonin release and result in c-cell hyperplasia, levels were monitored throughout the albiglutide clinical program.

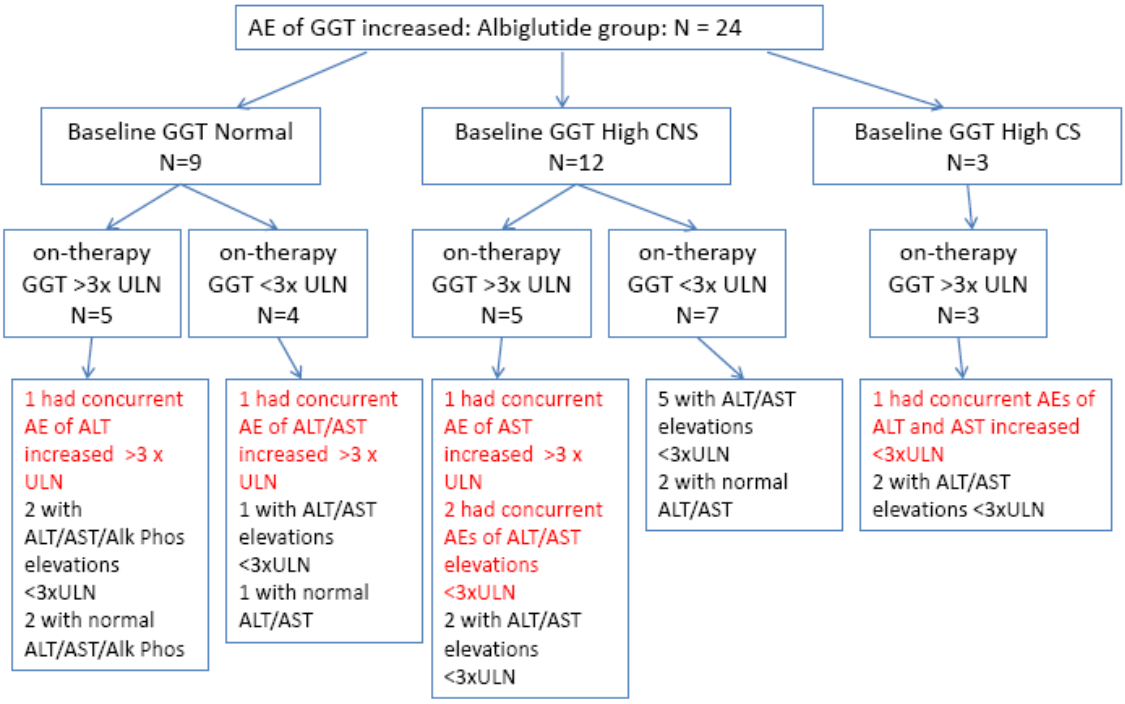
The applicant was asked to clarify whether baseline calcitonin levels were drawn for all subjects after implementation of a protocol amendment applied to Phase 3 studies, adding a baseline measurement and annually throughout the study. Followign this amendment, any subject found to have a baseline calcitonin value of >29.2 pmol/L (100 pg/mL) at Week –1 was discontinued from the study and underwent further evaluation. The applicant proposed that for subjects enrolled in studies prior to the amendment, a baseline calcitonin was retrospectively measured with an aliquot from a stored baseline serum sample, to which the division agreed.

Dr. Vasisht found seven subjects (3/1868 subjects in the albiglutide group and 4/2015 subjects in the all comparators group) who had calcitonin values of clinical concern (>29.2 pmol/L) at any on therapy visit. I have reviewed these cases and agree with her assessment that overall, there did not appear to be clinically relevant changes from baseline in calcitonin measurements.

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 (26/2116, 1.2% versus 15/ 2284, 0.7%). Figure 3 provides a schematic representation of albiglutide-treated subjects with elevated GGT levels.

Figure 3: P3-ISP AEs of Gamma Glutamyl Transferase in the Albiglutide Group



CS: clinically significant values (≥ 3XULN), CNS= clinically non-significant values (> baseline and < 3XULN)
Source: ISS Figure 40, Page 634.

As shown in the figure, 24 albiglutide-treated subjects had elevated GGT levels while on therapy. 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. In comparison, 14 comparator subjects had on therapy elevated GGT. Three of these 14 subjects had normal baseline values, and one subject had increased GGT values and an associated ALT/ AST >3 x ULN.

On further review, many events of hepatocellular injury in the albiglutide arm occurred in subjects with underlying cholestasis. Based on the data presented, the relationship between GGT elevations, cholestasis and liver injury remains unclear.

Hypoglycemia

In the Phase 3 trials, hypoglycemic events were classified based on American Diabetes Association (ADA) severity criteria. On-therapy hypoglycemic events were flagged by the investigator and classified for severity based on the 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 ≤70 mg/dL.
- **Asymptomatic hypoglycemia**: an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤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 ≤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.

At the time of NDA submission, pre-rescue hypoglycemic events were higher among subjects treated with albiglutide compared to placebo (11.9% vs. 7.3% of subjects, respectively).

Table 19: 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)	364
On therapy hypoglycemic event density[1]		80.24		50.54		17.33		25.36
Severity								
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
SAEs[2]								
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
Withdrawn due to hypoglycemic event[2]								
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.

As shown in Table 19, a lower proportion of subjects in the albiglutide group experienced pre-rescue hypoglycemia compared to all comparators (18.5% vs. 22.6 %, respectively). There were no hypoglycemic SAEs in the albiglutide arm and 4 subjects experienced 4 SAEs in the all comparators group. A small proportion of subjects were withdrawn from the study due to hypoglycemia (0.1% in both groups). In the albiglutide group, 7 subjects (0.3%) experienced 8 severe hypoglycemic events prior to hypoglycemic rescue, compared to 8 subjects (0.4%) experiencing 9 severe events of hypoglycemia in comparators. 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. There was a higher incidence of documented symptomatic hypoglycemic events in the comparator arm vs. albiglutide (16.3 % vs. 11.7%, respectively).

Albiglutide-treated subjects on background insulin or sulfonylureas experienced a greater incidence of hypoglycemic events compared to subjects not on hypoglycemia-inducing agents. Dr. Vasisht's review of the individual studies confirmed that in the monotherapy study, the incidence of severe and documented symptomatic hypoglycemia was similar between albiglutide 30 mg and placebo.

Gastrointestinal Events

Gastrointestinal (GI) adverse events occurring in ≥5% subjects across treatment groups are summarized in Table 20.

Table 20: On therapy Adverse Events in the Gastrointestinal Disorders System Organ Class Occurring in More Than 5% of Subjects in Either Treatment Group (P3-ISP)

	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[1]	n (%)	Number of AEs / Density[1]	n (%)	Number of AEs / Density[1]	n (%)	Number of AEs / Density 1
Gastrointestinal disorders								
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.

Dr. Vasisht's primary review of albiglutide's gastrointestinal adverse event profile focuses on albiglutide-treated patients compared with placebo, as the GI AE profiles of the active comparators could potentially affect 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 included 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. Overall withdrawals due to GI AEs were similar among albiglutide and placebo treated subjects (16/923, 1.7% for albiglutide and 8/423, 1.7% for placebo). 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.

In the following sections, I have reviewed gastrointestinal events of particular interest due either to their frequency in the Phase 3 trials or to the known AE profile of GLP-1 agonist drugs in general.

Diarrhea

Cases of diarrhea were generally mild in intensity in the albiglutide arm (73/121

subjects, 60.3%) 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 (3/49 subjects, 6.1%) vs. albiglutide (4/121, 3.3%). 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 (67/102, 65.7%) as well as the placebo group (33/45, 73.3%). There were no SAEs of nausea. A higher proportion of subjects in the placebo group (2/45, 4.4%) withdrew due to nausea, compared to subjects treated with albiglutide (3/102, 2.9%). Nausea resolved within one 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 among subjects treated wtih albiglutide compared to placebo (10.3 vs. 8.3%, respectively).

Renal impairment in patients with GI adverse events
GLP-1 agonists have been associated with severe nausea, vomiting and diarrhea resulting in dehydration leading to altered renal function. The most common adverse GI events noted with albiglutide (diarrhea, nausea, vomiting) have resulted in dehydration and hypovolemia with subsequent renal failure in other GLP-1 agonists. 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 led to a decline in renal function.

As described in Dr. Vasisht’s review, 32 subjects in total reported adverse events with a HLT of renal impairment (14 albiglutide-treated subjects versus 18 in the all comparators group). Of the 14 subjects in the albiglutide group, five had GI AEs around the time the AE of renal impairment was reported. These events were non-serious, mild or moderate intensity and did not result in study drug withdrawal. I have reviewed these five cases individually, and I agree with Dr. Vasisht’s assessment that, from the information provided, a safety signal for GI events leading to renal impairment cannot be established.

<u>Immunogenicity</u>
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 response caused diminished exposure to albiglutide and was associated with type 3 hypersensitivity reactions (immune complex deposition) in a subset of animals.

Immunogenicity was evaluated in 2,934 albiglutide treated subjects in 15 clinical studies (8 Phase 3, 2 Phase 2b, and 5 Phase 1/2a studies). Samples were collected at regular 12-week intervals 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 3

studies, antibody measurements were not conducted for subjects receiving placebo or comparator treatments (except in study GLP112756, where 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 two switch studies, additional immunogenicity samples were collected at Week 116 and Week 142, reducing the sampling interval from every 24 to every 12 weeks.

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 one post-dose sample tested positive for anti-albiglutide antibodies.

Clinical Immunogenicity Results
2934 subjects received at least one dose of study drug across the clinical program. Of these, 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. In addition,128/2934 subjects (4.4%) developed treatment-emergent anti-albiglutide antibodies after at least one dose.

The applicant's 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). As explained in Dr. Vasisht's review, using the pooled data from the Phase 3 trials, there was no interaction (p-value >0.1) between reduction in HbA1c and presence of anti-albiglutide antibodies, regardless of whether the antibodies were neutralizing or crossreacting with native GLP-1.

Serious adverse events in antibody-positive subjects
The proportion of SAEs was relatively balanced between antibody-positive and negative subjects (15/116, 12.9% versus 220/1927, 11.4% respectively). The most common SAE in anti-albiglutide antibody-positive subjects occurred in the cardiac and nervous system disorders SOC (4/116, 3.4%). 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). These are described below.

Injection Site Reactions

Albiglutide vs. Placebo

As shown in Table 21, a higher proportion of subjects in the albiglutide treatment group experienced an ISR compared with placebo-treated subjects (17.6% vs. 7.5%). These events were most 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 23/162, 14.2% versus placebo 8.6% 3/35, 8.6%) and a few subjects reported >20 events each (albiglutide 11/162, 6.8% versus placebo 3/35, 8.6%). As noted in Dr. Vasisht's review, relatively few subjects accounted for a large number of events; 23 subjects in the albiglutide group had approximately 620 events (12 subjects with 11-20 events plus 11 subjects with >20 events). Details regarding ISRs in this group are provided below in Table 21 (Albiglutide vs. All Comparators).

Table 21: On therapy Injection Site Reaction Characteristics Overall - Albiglutide versus Placebo (P3-ISP)

	Placebo	Albiglutide
	N=468	N=923
	n (%)	n (%)
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)
Maximum intensity per subject		
n	35	162
Mild	33 (94.3)	118 (72.8)
Moderate	2 (5.7)	41 (25.3)
Severe	0	3 (1.9)
Number of events	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, as shown in Table 22. Seven subjects in the albiglutide group had a preferred tem of injection site hypersensitivity, compared with none in the placebo arm.

Table 22: On therapy Injection Site Reactions Occurring in More than 2 Subjects for Albiglutide Versus Placebo

System Organ Class Preferred Term	Placebo (N=468)	Albiglutide (N=923)
	n (%)	n (%)
Any injection site reaction	35 (7.5)	162 (17.6)
General Disorders and administration site		
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

In the P3-ISP, 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 of these subjects withdrew from study drug, and four subjects had single events, while five 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 ISRs each.

Albiglutide vs. Active Injectable Comparators (Liraglutide, Insulin Lispro and Insulin Glargine)

23 presents a summary of the characteristics of on-therapy ISRs in the three active comparator open label studies conducted with injectables (liragluitide, 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 three 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 (range:127.7-360.1 days) compared with the active comparator groups (39.4- 213.7 days).

Table 23: On-therapy Injection Site Reactions: Albiglutide Versus Active Comparators (Injectables)

	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[1], n (%)	16 (4.0)	5 (1.2)	8 (2.8)	0	18 (3.6)	0
No. events	188	37	135	22	488	57
Intensity of event, n (%)						
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
Duration (days)[2]						
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[3]						
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[4]						
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 negative for anti-albiglutide antibodies,

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 multiple ISRs regardless of antibody status, the proportion of subjects with more than 20 ISRs was greater among anti-albiglutide antibody-positive subjects (12.8% versus 4.4% antibody-negative). ISR discontinuations in antibody-positive subjects occurred in 5/45 subjects.

Table 24: Injection Site Reactions by Post-dose Anti-Albiglutide Antibody Status

	Anti-Albiglutide Antibody Positive	Anti-Albiglutide Antibody Negative
	(N=116)	(N=1927)
Number of subjects with reaction	47 (40.5)	274 (14.2)
Number of events	452	1286
Number of events per subject[1]		
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)
Maximum intensity of events per		
Mild	31 (66.0)	209 (76.2)
Moderate	16 (34.0)	59 (21.5)
Severe	0	6 (2.2)
Median onset (days) of event		
Relative to first dose	190	274
Relative to preceding dose	0	1.0
Median duration (days) of event[3]	6.0	7.0
Action taken		
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

Systemic Allergic Reactions

The overall proportion of SARs were balanced for the albiglutide vs. placebo group (1.8% versus 1.9%, respectively) as well as albiglutide vs. all comparators (1.5% versus 1.2%). The highest proportion of events occurred in the skin and subcutaneous disorders SOC for both treatment comparison groupings, and these were balanced between treatment arms.

Table 25 shows 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% albiglutide-treated versus 1.2%), with urticaria being the most common event in both groups (0.8% versus 0.7%). Among subjects receiving albiglutide, three experienced episodes of angioedema, as did three in the all comparators group. I have reviewed these cases among albiglutide-treated subjects, and none were life threatening, although a causal link to albigutide cannot be ruled out. One patient in the albiglutide-treated group experienced an episode of anaphylaxis.

Table 25: On therapy SARs - Albiglutide versus All Comparators, with at least 1 event in the albiglutide group with higher frequency compared to 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
Skin and subcutaneous tissue disorders				
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
Eye disorders				
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
Gastrointestinal disorders				
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
General disorders and administration site conditions				
Any event	0	1 (0.0)	1 (0.0)	1 / 0.03
Face edema	0	1 (0.0)	1 (0.0)	1 / 0.03
Immune system disorders				
Any event	1 (0.0)	1 (0.0)	1 (0.0)	1 / 0.03
Anaphylactic reaction	0	0	1 (0.0)	1 / 0.03
Respiratory, thoracic, and mediastinal disorders				
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.

Pancreatitis

In the Phase 3 program, investigators were instructed to monitor subjects for symptomatology suggestive of pancreatitis (e.g., persistent and/or severe abdominal pain, nausea, and vomiting) and to report all suspected cases. Overall, there was an imbalance between serious events of pancreatitis in the albiglutide arm (3 events, 0.2%, versus none in placebo). The Pancreatitis Adjudication Committee (PAC) adjudicated 47 cases of interest (23 AE/SAEs suspicious for pancreatitis and 24 abnormal lipase measurements ≥3 × ULN) across the 8 Phase 3 studies. Of these 47 cases "definite or probable pancreatitis" with at least a possible relationship to study treatment was 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 Phase 3 studies, the cumulative (through the 4MSU) incidence rate of pancreatitis for albiglutide was 1.4/1,000 person-years, compared with 0.4/1,000 in all comparators and 7.1/1,000 in liraglutide. In the program, one subject treated with albiglutide had a fatal event of necrotizing pancreatitis that was related to an ERCP procedure.

Pancreatic Enzymes
Study GLP114179 was the only Phase 3 study that assessed on-therapy amylase and lipase levels at scheduled time periods (screening, week 12 and week 32). Amylase or lipase values ≥ 3×ULN were pre-defined as 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.

As shown in Dr. Vasisht's review, In GLP114179 mean amylase and lipase levels were similar at baseline and Week 32 between albiglutide- and liraglutide-treated subjects. Please refer to her review for additional information regarding monitoring of pancreatic enzymes in the albiglutide Phase 3 program.

Diabetic Retinopathy
As described in Table 26, a higher incidence of retinopathy was observed in albiglutide-treated subjects when compared to placebo (3.6 % vs. 1.7%, respectively). The majority of events were considered background retinopathy, with a small percentage of subjects (<1%) developing proliferative retinopathy. As Dr. Vasisht points out, data for dose effects are confounded by small event numbers in the forced titration study. In addition, the applicant notes that fundoscopy was not conducted in a rigorous manner, and therefore baseline retinopathy status may not have been accurately captured.

The proportion of subjects with investigator-identified diabetic retinopathy was 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 26: 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
On therapy Diabetic Retinopathy Events								
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								
Severity								
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
Treatment								
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

Laboratory Data

Pancreatic enzymes, hepatic enzymes, serum GGT levels and serum calcitonin values of clinical concern have been previously discussed 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. 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, and there did not appear to be a treatment-related effect on hematology parameters.

In the renal study, significant changes were observed in a greater proportion of albiglutide-treated subjects than sitagliptin-treated subjects for hematocrit (7/249, 3.2% versus 4/246, 1.9%) and hemoglobin (8/249, 3.7% vs. 3/246, 1.5%, respectively) values.However, subjects with clinically significant changes were more likely to have had abnormal values at baseline.

Chemistry

There was no evidence of any clinically meaningful mean changes from baseline for any of the general chemistry parameters across comparison groups.

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.

Liver function tests

Mean values for ALT, AST, alkaline phosphatase, and bilirubin 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 or alkaline phosphatase.

Vital Signs

Blood Pressure

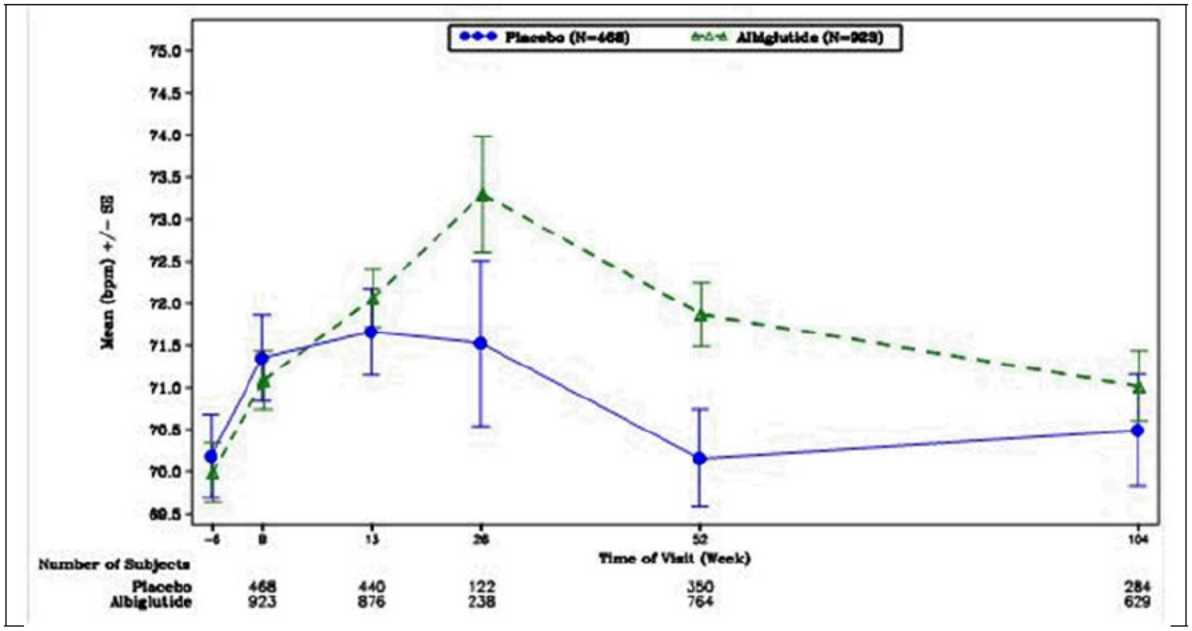
Mean changes in systolic and diastolic blood pressure varied within $\pm$1 mmHg over time in the albiglutide, placebo and active comparator groups. In those subjects not taking potentially confounding blood pressure lowering medication mean systolic blood pressure change from baseline at weeks 13 and 26 was within 1 mmHg of baseline values, and comparable in albiglutide-treated subjects compared with the all comparators group.

In study GLP112756, in which subjects underwent forced up-titration from 30 mg/week to 50 mg/week titration, an albiglutide-related dose response in blood pressure was not noted. Blood pressure changes from baseline in the 50 mg/week albiglutide group were comparable to the placebo group.

Heart Rate

Heart rate data was assessed by pulse rate and digital ECGs. Mean heart rate derived from vital signs assessments were generally 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, as shown in Figure 4 (treatment difference range of 0.8 to 1.4 bpm at weeks 13, 52 and 104, respectively). 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).

Figure 4 Mean Heart Rate Over Time From ECG Recordings for Albiglutide Versus Placebo Group (Phase 3 Integrated Safety Populations)



Source Data: 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 da ta through Week 104, partial data after Week 104.

Heart rate by dose

Up-titration from 30 to 50 mg resulted in a 1-2 bpm increase in heart rate (range 0.5-1.7 bpm). In GLP112756, in which uptitration was forced at Week 12, heart rate data derived from ECGs showed that albiglutide increase 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 also demonstrated that albiglutide uptitration from 30 mg to 50 mg/week resulted in an approximate 1-2 bpm increase in heart rate.

Electrocardiograms

As shown in Dr. Vasisht's review, the P-R interval in subjects treated with albiglutide showed a small increase over all comparators (≤1 msec) at week 52 and 104, and the R-R interval showed larger decreases for albiglutide compare to all comparators. Up-

titration to 50 mg albiglutide was not associated with any adverse change in ECG parameters.

The applicant's thorough QT Study was reviewed by the Interdisciplinary Review Team for QT Studies. The team found no significant QTc prolongation effect of albiglutide at either the 30 or 50 mg doses. 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.

Special Populations

Renal disease

In the P3-ISP, the proportion of subjects who experienced any AE across 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. There was a trend toward 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 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) of those with moderate renal impairment experienced an on-therapy AE. Among all comparators, 79.3% (715/902) of subjects with normal renal function, 80.9% (976/1207) of those with mild renal impairment, and 85.1% (148/174) of those with moderate renal impairment experienced an adverse event. There was one subject who experiened severe impairment of renal function in the all comparators group and none in the albiglutide group.

Of note, a trend toward increased frequency of nausea and vomiting was seen as renal function decreased. Among albiglutide-treated patients, 9.8% (79/804) of subjects with normal renal function developed nausea, compared with 11.9% (136/1139) for those with mild impairment, and 16.2% (28/173) of those with moderate impairment. Among comparators, 9.1% (82/902) of subjects with normal renal function, 11.1% (134/1207) with mild impairment, and 14.9% (26/174) of those with moderate impairment developed nausea.

The prevalence of vomiting was 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 function for albiglutide 3.7 % (30/804) and all comparators 4.0 % (36/902), and for mild impairment, 5.4% in albiglutide-treated subjects (62/1139) versus 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 versus 4% (7/174) in all comparators.

Renal Study GLP114130

As Dr. Vasisht describes in her review of the applicant's renal study, adverse events in both treatment groups were mostly 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.

Table 27 Overview of Adverse Events (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[2]	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[3]	6 (4.7)	17 (16.7)	3 (15.8)	4 (3.1)	15 (14.9)	7 (41.2)
Any AE by max intensity[4]						
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[5]						

Source Data: 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*(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.

• Advisory Committee Meeting

This application was not discussed before an advisory committee.

• Pediatrics

The proposed pediatric study plan was reviewed by the pediatric review committee on January 22, 2014. The pediatric review committee was in agreement with the following study plan:

- The pediatric study requirement for ages 0 through 9 years will be waived because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.

- The submission of the pediatric studies for ages 10 to 17 years for this application will be deferred because this product is ready for approval for use in adults and the pediatric study have not been completed.

The deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act will be required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required studies are listed below.

- *A single study of albiglutide in pediatric patients with T2DM,* (b) (4) [redacted] *pediatric subjects aged >10 and <18 years.*

(b) (4) [redacted]

Dates for: Final Protocol Submission, Study/Trial Completion, Final Report Submission are being negotiated at this time. The timeline for this combined PK/PD and safety/efficacy study will be in keeping with precedent applications for type 2 diabetes and strive toward ensuring a timely assessment of the efficacy and safety of albiglutide in children.

- **Other Relevant Regulatory Issues**

None identified.

• Labeling

Labeling discussions are ongoing at the time of this review. Key issues are summarized below. Please see the final label for further details.

- Changes have been made to the ***Warnings and Precautions*** section of the label, including inclusion of information regarding hypersensitivity reactions. In addition, consideration should be given to adding atrial fibrillation/atrial flutter to this section given the signal found among albiglutide-treated patients in the Phase 3 program (at the time of this review, these can be found in ***Adverse Reactions***.

- Extensive changes have been made to the ***Adverse Reactions*** section of the label. These were primarily to emphasize findings of pneumonia, appendicitis, and GGT elevations not in favor of albiglutide.

- Information regarding albiglutide's effect on fasting and postprandial glucose excursions as well as mean heart rate changes have been added to ***Clinical Pharmacology***. Data from drug interaction trials (co-administered drugs included simvastatin, digoxin, oral contraceptives, and warfarin) has been added to this section as well.

- ***Clinical Studies*** has been significantly revised, conforming to the style of other recently-approved Physician's Labeling Rule-formatted labels for diabetes drugs. The applicant has been asked to (b) (4)

- Inappropriate promotional statements have been revised with input from the Division of Drug Marketing, Advertising, and Communications (DDMAC); formatting has been reviewed by the Study Endpoints and Label Development (SEALD) group to ensure consistency with the Physician's Labeling Rule.

• Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval, pending agreement on final labeling

- Risk Benefit Assessment

The data in the NDA support an overall conclusion that use of albiglutide in patients with T2DM offers benefits that are not outweighed by the risk associated with use of the drug.

Benefit

Albiglutide provides clinically meaningful reductions in glycemia in the monotherapy, add-on to single agent therapy, and add-on to dual agent therapy settings.
In the monotherapy setting, albiglutide (30 mg and 50 mg) trended towards offering significantly greater glucose lowering than placebo (GLP112756, Wek 104 LOCF). In the add-on setting, albiglutide provided significantly greater glucose lowering than a sulfonylurea or a DPP-4 inhibitor (GLP112753) at trial end (Week 104 LOCF). The magnitude of the glycemic reduction seen for both doses of albiglutide is similar to the glucose lowering expected of other currently approved GLP-1 agonists. In contrast to insulin and insulin secretagogues, albiglutide poses a relatively small risk of hypoglycemia. In contrast to insulin and insulin secretagogues, albiglutide causes less weight gain.

Risks

Several risks associated with the use of albiglutide were identified in the program.

In its development program, there was an imbalance not in favor of albiglutide for SAEs of atrial fibrillation compared with all comparators (9/2116, 0.4% versus 2/2284, 0.1%), and in addition, two SAEs of atrial flutter were discovered for albiglutide (none among all comparators). A review of the 11 cases among albiglutide-treated patients identifies several with underlying conditions that would predispose to arrhythmias, and the applicant has identified these arrhythmia events as an important identified risk; however, it has suggested inclusion in “Adverse Events.” I have also reviewed non-serious treatment-emergent adverse events for atrial fibrillation/flutter, and as described previously in this review, again there is an imbalance not in favor of albiglutide, including 27/2116 (1.3%) patients on study drug compared with 14/2284 (0.6%) of those among all comparators. Despite the fact that many patients who developed atrial fibrillation/flutter did have predisposing conditions, given the imbalance and the potentially fatal outcomes associated with these arrhythmias, it is my opinion that they should be considered for inclusion in “Warnings and Precautions” rather than “Adverse Events.”

In addition, there was a higher proportion of subjects treated with albiglutide who developed on-therapy (serious and non-serious) events of pneumonia compared with placebo (17/923, 1.8% versus 3/468, 0.6%) and all comparators (37/2116, 1.8% versus 18/2284, 0.8%). Of these, there was an imbalance not in favor of albiglutide for SAEs, with 12/2116 (0.5%) in the treatment group versus 3/2284 (0.2%) among all comparators. I have reviewed the SAEs of pneumonia; all patients were hospitalized and recovered with treatment. However, the majority lacked sufficient information regarding relevant risk factors. At this point, I am in favor of leaving pneumonia in the “Adverse Events” section of the label but recommend following it as an AE of interest in the postmarketing studies.

Similarly, there was a higher proportion of subjects in the albiglutide arms who developed on-therapy appendicitis events compared with all comparators. In the Phase 3 studies, 5/2116 (0.2%) of albiglutide-treated patients developed appendicitis, compared with none among all comparators. There is not a clear mechanistic link

between albiglutide and development of appendicitis, but the imbalance is notable and although all patients recovered following surgery, there is no question it is a condition of medical concern. Given the relatively low number of cases overall (especially when considering rates of appendicitis in the general population are similar), I recommend inclusion in “Adverse Events” with follow-up as an AE of interest in postmarketing trials.

An imbalance not in favor of albiglutide for hypersensitivity reactions were observed in the Phase 3 trials, including SARs of anaphylaxis, angioedema, and rash. Hypersensitivity is labeled in the warnings and precautions of the three other approved GLP-1 agonist labels based on postmarketing reports of serious reactions. While the majority of the events discovered in the albiglutide program were not life threatening, hypersensitivity should be included as a warning in the product label.

Patients receiving albiglutide trended toward higher GGT values than those in all comparator groups. While the clinical relevance has not been fully elucidated, this imbalance should be labeled as an adverse reaction and monitored in postmarketing studies to better elucidate a potential relationship.

While the applicant’s dedicated renal study (GLP114130) did not reveal any significant concerns with use of albiglutide in patients with mild or moderate renal impairment, an increased incidence of gastrointestinal adverse events was observed in patients with severe renal impairment. A full evaluation of this effect was limited by the small sample size in the albiglutide (N=19) and comparator (sitagliptin, N=17) groups, but renal impairment has been reported in postmarketing studies with other GLP-1 agonists and therefore warrants inclusion in the warnings and precautions section of the label.

The cardiovascular safety of albiglutide was evaluated with a formal evaluation of major cardiac adverse events based upon the 1.8 risk margin set forth in the FDA Diabetes Guidance. As previously discussed, the upper-bound of the alpha-adjusted 97.55% confidence interval of the hazard ratio meets the pre-marketing criteria for ruling out an 80% relative increase in CV risk; MACE will be further evaluated as part of a required postmarketing cardiovascular outcomes trial (see below).

Although there were no signals in the Phase 3 program to show that albiglutide otherwise behaves differently from other in-class products, as with all approved GLP-1 agonists, the label should include warnings regarding the class risk of thyroid c-cell tumors (included in other labes as a boxed warning) pancreatitis, hypoglycemia when used in combination with insulin secretagogues or insulin, complications in patients with severe gastrointestinal disease, and lack of evidence of macrovascular risk reduction.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

At the time of this review, a postmarketing REMS is being considered by the Office of Surveillance and Epidemiology, and final recommendations will be included as an addendum to this review.

- Recommendation for other Postmarketing Requirements and Commitments

The following post-marketing studies will be required under FDCA 505(o)3 (at the time of this review the dates and final language for some of the postmarketing required studies are under discussion).

Clinical postmarketing requirements:

- *A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of TANZEUM (albiglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of TANZEUM (albiglutide).*
- *A randomized, double blind, placebo-controlled trial evaluating the effect of TANZEUM (albiglutide) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus (T2DM). The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with albiglutide to that observed in the placebo group is less than 1.3.*

  The study should include the following Adverse Events of Special Interest: development of thyroid tumors, pancreatic cancer, overall injection site reactions, serious hypoglycemia events, serious gastrointestinal events, hepatic events, pancreatitis, and serious hypersensitivity reactions. In addition the following adverse events should be monitored in your CVOT: appendicitis, pneumonia, atrial fibrillation/flutter, diabetic retinopathy, liver toxicity and imbalances in hepatic enzymes including gamma-glutamyl transpeptidase (GGT) levels and the development of renal impairment in subjects with gastrointestinal adverse events. Immunogenicity data and the development of anti-drug antibodies should also be collected with any relationship to reduced efficacy, injection site reactions and hypersensitivity reactions.

- *A study evaluating gallbladder ejection fractions in albiglutide treated subjects is recommended to further characterize* (b) (4)

(b) (4)

- *A randomized and controlled pediatric study under PREA to evaluate the safety, efficacy, and pharmacokinetics of TANZEUM (albiglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10-17 years (inclusive).*

CMC Postmarketing Commitments

- *To develop, validate and implement an ultra-performance liquid chromatography (UPLC) analytical method to assess purity for release and stability of drug substance and drug product.*

- *To develop, validate, and implement an FcRN binding assay to monitor functionality of human albumin portion of drug substance and drug product for release and stability.*

CMC/Micro Postmarketing Commitments

- *Develop and validate a reliable endotoxin test for the albiglutide drug product in-process and release samples and include worst-case hold conditions in the relevant containers.*

- *Conduct studies to develop an understanding of the mechanism of low endotoxin recovery in the formulated drug substance and drug product.*

- Recommended Comments to Applicant

None

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

/s/

ALI MOHAMADI
04/11/2014

JEAN-MARC P GUETTIER
04/11/2014
I concur with Dr. Mohamadi's recommendations.