

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125431Orig1s000**

**SUMMARY REVIEW**

Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Jean-Marc Guettier
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	125431
<b>Supplement #</b>	
<b>Applicant Name</b>	GlaxoSmithKline LLC.
<b>Date of Submission</b>	January 14, 2013
<b>PDUFA Goal Date</b>	April 15, 2014
<b>Proprietary Name / Established (USAN) Name</b>	TANZEUM (albiglutide)
<b>Dosage Forms / Strength</b>	
<b>Proposed Indication(s)</b>	1. 2. 3.
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted OND Action Package, including:</b>	<b>Names of discipline reviewers</b>
Medical Officer Review	Kaveeta Vasisht, MD, Pharm.D.
Statistical Review	Japobrata Chouhury, PhD and Bo Li, PhD and Mark Rothman PhD
Pharmacology Toxicology Review	Ronald Wange, PhD
CMC Review/OBP Review	Joao Pedras-Vasconcelos, PhD
Microbiology Review	Bo Chi, PhD and Lakshmirani Narasimhan, PhD
Clinical Pharmacology Review	Ritesh Jain, PhD
OPDP	Kendra Jones
DSI	Cynthia Kleppinger, MD
CDTL Review	Ali Mohamadi, MD
OSE/DMEPA	Yelena Maslow Pharm.D., Augustin Reasol Pharm.D., Sarah Vee Pharm.D.
OSE/DRISK	Joyce Weaver Pharm.D.

OND=Office of New Drugs  
 OPDP=Office of Prescription Drug Promotion  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DSI=Division of Scientific Investigations  
 DDRE= Division of Drug Risk Evaluation  
 DRISK=Division of Risk Management  
 CDTL=Cross-Discipline Team Leader

## Division Director Memorandum

### 1. Introduction

On January 14, 2013 GlaxoSmithKline LLC submitted a Biologics License Application (BLA) for Tanzeum under section 351 of the Public Health Service Act. The applicant is seeking to indicate Tanzeum as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Tanzeum is a solution for injection containing either 30 or 50 mg of albiglutide [i.e., a glucagon-like peptide 1 (GLP-1) receptor agonist]. Tanzeum is to be administered by subcutaneous injection at once weekly intervals. If approved, Tanzeum will be the fourth GLP-1 agonist indicated for use in the management of patients with type 2 diabetes mellitus in the United States.

This document serves as the division director's memorandum for the application.

### 2. Background

Albiglutide is a recombinant protein biosynthesized using a genetically modified strain of *Saccharomyces cerevisiae*. The albiglutide molecule consists of two fused copies of GLP-1 (fragment 7-36) genetically linked to the (b) (4) recombinant human serum albumin (HSA). The GLP-1 sequence has been modified at position 8 to confer resistance to proteolysis and prolong GLP-1 action in vivo. Albiglutide was demonstrated to bind and activate the GLP-1 receptor. The biological effects of endogenous GLP-1 on glucose homeostasis include augmentation of glucose stimulated insulin secretion, inhibition of glucagon release, and delaying gastric emptying. These effects in concert are believed to contribute to the glucose lowering effect of exogenously administered GLP-1 agonists in general and albiglutide specifically.

Potential and labelled risks of currently available long-acting GLP-1 therapies include: The potential risk of thyroid C-cell tumors including medullary thyroid carcinoma, the risk of acute pancreatitis, the risk of worsening renal function precipitated by dehydration due to product related gastrointestinal adverse reactions and the risk of increased hypoglycemia when used in combination with drugs known to cause hypoglycemia (i.e., sulfonylurea or insulin). Risks for currently approved products are managed through product labeling and Risk Evaluation and Mitigation Strategies (REMS) to ensure that in patients prescribed long acting GLP-1 therapies benefits related to improved glycemic control of the drug are not outweighed by these risks.

The phase III clinical development program for albiglutide was discussed with the Division of Metabolism and Endocrinology Products (DMEP) at an End of Phase II Meeting on August 12, 2008 and in the form of written correspondences reviewed in Table 2 of Dr. Vasisht's review. The

development program included a prospective proposal to assess cardiovascular risk associated with albiglutide use to satisfy the requirements stipulated in the 2008 FDA Guidance for Industry entitled: *Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. The proposed plan was reviewed by DMEP as reflected in an advice letters issued on July 1<sup>st</sup> and 23<sup>rd</sup> 2010 and a response from the sponsor received on October 1<sup>st</sup> 2010.

### 3. CMC/Device

I concur with the conclusions reached by the chemistry and microbiological product quality reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 12 months at 2 – 8°C, ambient humidity, protected from light followed by 1 month at 30°C.

A recent issue that has not been captured in the manufacturing process and microbiological control and microbiology product quality primary reviews is discussed below. This issue is reviewed in greater details by Drs. Pedras-Vasconcelos, Narashimhan and Chi in recently filed addenda<sup>1</sup> to their reviews.

On March 20, 2014, Dr. Patricia Hughes, team leader for the Biotechnology Manufacturing Assessment Branch (BMAB) within the Office of Medical Product Quality received an email from Andrew Jones, the Head of Quality for Biopharm Supply Chain at GSK, to alert the Agency that (b) (4)

[Redacted]

[Redacted] (b) (4)

In response to FDA questions, GSK submitted amendments to the BLA on March 28, 2014 and April 8, 2014 summarizing the risk that this new process-related impurity poses to drug quality, sterility and

<sup>1</sup> Refer to DARRTs documents dated 4/10/2014 and 4/10/2014 by these authors.

<sup>2</sup> Specifically, at the time of [Redacted] (b) (4)

Drs. Lakshmi Narasimhan, Ph.D. (BMAB), Bo Chi, Ph.D. (BMAB) and Joao Pedras-Vasconcelos, Ph.D (Office of Biotechnology Products, Division of Therapeutic Proteins) have reviewed these data and concur that the recently identified in-process impurity would not impact product quality, microbiology/sterility and safety and continue to recommend approval. Several post-marketing commitment with regard to this issue have been agreed upon and will be included in the approval letter.

#### **4. Nonclinical Pharmacology/Toxicology**

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

#### **5. Clinical Pharmacology/Biopharmaceutics**

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The PK of albiglutide in T2DM subjects was studied following a single dose subcutaneous administration of 30 mg. Albiglutide was observed to have a prolonged terminal half-life of approximately 5 days and reaches steady-state exposures after 4 to 5 weeks of once-weekly administration. Exposures for the 30 mg and 50 mg dose levels were dose-proportional. Subcutaneous administration of albiglutide in the abdomen, thigh, or upper arm resulted in similar exposure and albiglutide can be administered in either sites. Gastrointestinal adverse reactions and heart rate increase were shown to be dose dependent and 30 mg once weekly is recommended as the starting dose of albiglutide with the option to uptitrate to 50 mg once weekly for patients who do not achieve adequate glucose lowering with the 30 mg dose.

#### **6. Clinical Microbiology**

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval. See reviews by Bo Chi, PhD and Lakshmirani Narasimhan, PhD for full details.

#### **7. Clinical/Statistical-Efficacy**

To support the indication of improved glycemic control, the medium to long term glucose lowering effect of albiglutide was evaluated in 8 phase 3 clinical trials.

The pivotal trials were multi-center, multi-national, randomized, double-blind (n=5) or open-labeled (n=3) and the primary comparison was against placebo (n=4) or an active comparator (n=4). Studies

were divided into four periods comprising a pre-screening/screening period, a run-in/stabilization period, a treatment period and an 8 weeks post-treatment follow-up period. The variable used in the primary efficacy assessment was the difference in the change in hemoglobin A1c (i.e., HbA1c) from baseline to trial end between albiglutide-treated subjects and comparator-treated subjects.

The timing of the primary efficacy assessments ranged between 26 to 104 weeks. Inclusion and exclusion criteria were similar between trials and are reviewed by Dr. Vasisht. Inadequate glycemic control at baseline (i.e., HbA1c between 7 and 10.5%) in spite of dietary intervention, lifestyle intervention or maximally effective background therapy (ies) was a key eligibility criterion in all trials. Only one trial (i.e., **114130**) enrolled patients with moderate renal impairment (creatinine clearance less than or equal to 60 mL/min) in all other trials these subjects were excluded.

In six out of eight trials, albiglutide was initiated at a dose of 30 mg once weekly and investigators had the option to increase the dose to 50 mg once weekly, if additional glucose lowering was needed (time point not proscribed except for a prohibited period at the beginning of treatment). In one trial (i.e., **112756**), doses of 30 mg and 50 mg once weekly were compared head to head. The design features, primary endpoint and timing of the efficacy assessment in the albiglutide phase III pivotal trials conform with the Guidance for Industry entitled *“Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention”* and are appropriate to support an indication of improved glycemic control. No study design or execution issues with the potential to invalidate the study results were noted in the reviews or at inspections.

The efficacy of albiglutide was assessed in various, relevant, clinical use settings that included;

- Albiglutide used as **monotherapy** in drug naïve adult subjects with type 2 DM not optimally controlled at baseline on diet and exercise alone.
  - Double Blind **Trial 112756** - Efficacy assessment at **52 weeks**
  - Compared **albiglutide** 30 mg and 50 mg weekly to **placebo**
  - All subjects continued in a 104 weeks double-blind controlled extension
  - At NDA submission, subjects had completed at least 2 years (Data cut-off 03/08/2012)
- Albiglutide used as **add-on therapy to background metformin** in adult subjects with type 2 DM not optimally controlled at baseline on  $\geq 1500$  mg/day of metformin
  - Double Blind **Trial 112753** - Efficacy assessment at **104 weeks**
  - Compared **albiglutide** (30 mg weekly with option to uptitrate to 50 mg weekly) first to **placebo**, then to glimepiride 4 mg daily and sitagliptin 100 mg daily.
  - All subjects continued in a 52 weeks double-blind controlled extension
  - At NDA submission, subjects had completed at least 2 years (Data cut-off 02/27/2012)
- Albiglutide used as **add-on therapy to background metformin with or without a sulfonylurea** in adult subjects with type 2 DM not optimally controlled at baseline on  $\geq 1500$  mg/day of metformin with or without a sulfonylurea (e.g., in 112757 equivalent to glimepiride  $\geq 4$  mg).

- Open Label **Trial 112754** - Efficacy assessment at **52 weeks**
- Compared **albiglutide** (30 mg weekly with option to uptitrate to 50 mg weekly) to **insulin glargine** (titrated per protocol).
- All subjects continued in a 104 weeks open label controlled extension
- At NDA submission, subjects had completed at least 2 years (Data cut-off 03/01/2012)
  
- Double Blind **Trial 112757** - Efficacy assessment at **52 weeks**
- Compared **albiglutide** (30 mg weekly with option to uptitrate to 50 mg weekly) to **pioglitazone** (30 mg daily with option to uptitrate to 45 mg daily).
- All subjects continued in a 104 weeks double-blind controlled extension
- At NDA submission, subjects had completed at least 2 years (Data cut-off 02/22/2012)
  
- Albiglutide used as **add-on therapy to background metformin with or without a thiazolidinedione** in adult subjects with type 2 DM not optimally controlled at baseline on  $\geq 1500$  mg/day of metformin with or without a thiazolidinedione used at doses equivalent to  $\geq 30$  mg/day of pioglitazone.
  - Double Blind **Trial 112755** - Efficacy assessment at **52 weeks**
  - Compared **albiglutide** (30 mg weekly no uptitration) to **placebo**.
  - All subjects continued in a 104 weeks double-blind controlled extension
  - At NDA submission, subjects had completed at least 2 years (Data cut-off 12/20/2011)
  
- Albiglutide used as **add-on therapy to one or multiple (i.e., up to three) oral anti-diabetic drugs** (i.e., metformin, sulfonylurea and thiazolidinediones).
  - Open Label **Trial 114179** - Efficacy assessment at **32 weeks**
  - Compared **albiglutide** (30 mg weekly with forced uptitration to 50 mg weekly at Week 6) to **liraglutide** (titrated per protocol from 0.6 to 1.8 mg daily).
  - No extension
  - At NDA submission, subjects had completed the trial (Database lock 10/28/2011)
  
- Albiglutide used as **add-on therapy to basal insulin with or without oral anti-diabetic drugs**.
  - Open label **Trial 108486** - Efficacy assessment at **26 weeks**
  - Compared **albiglutide** (30 mg weekly with option to uptitrate to 50 mg weekly) to **lispro** (uptitration based on self-monitored glucose results and as appropriate per standard of care).
  - All subjects continued in a 26 weeks open-label controlled extension
  - At NDA submission, subjects had completed the trial (Database lock 3/12/2012)
  
- Albiglutide used **with or without oral anti-diabetic drugs in patients with baseline moderate renal impairment**.
  - Double-blind **Trial 114130** - Efficacy assessment at **26 weeks**
  - Compared **albiglutide** (30 mg weekly with option to uptitrate to 50 mg weekly) to **sitagliptin** [per appropriate renal dose (25, 50 or 100 mg per day)].
  - All subjects continued in a 26 weeks double-blind controlled extension

- At NDA submission, subjects had completed the trial (Database lock 6/15/2012)

The primary efficacy results for these eight pivotal trials, reproduced and modified from Table 6 in Dr. Mohamadi' s CDTL memorandum are shown below.

**Table 1: Change in HbA1c from baseline to end of trial in the mITT population using LOCF to impute missing data.**

Study (Weeks)	Treatment Arm	n	Baseline Mean ± SD	LS Mean Change ± SE	LS mean difference (95% CI) Albiglutide minus Comparator	p-value*
<b>Monotherapy and Dose-Response Trial</b>						
<b>112756 (52)</b>	Albiglutide 30	100	8.05 ± 0.9	-0.70 ± (1.0)		
	Albiglutide 50	97	8.21 ± 0.9	-0.89 ± (0.1)		
	Placebo	98	8.02 ± 0.9	+0.15 ± (0.1)	<b>-0.84 (-1.11, -0.58)<sup>#</sup></b> <b>-1.04 (-1.31, -0.77)<sup>§</sup></b>	<.0001 <.0001
<b>Add-on to background metformin</b>						
<b>112753 (104)</b>	Albiglutide	293	8.09 ± 0.8	-0.63 ± 0.1		
	Placebo	97	8.12 ± 0.9	0.27 ± 0.1	<b>-0.91 (-1.16, -0.65)</b>	<.0001
	Glimepiride	299	8.12 ± 0.8	-0.36 ± 0.1	<b>-0.27 (-0.45, -0.09)</b>	<.0001
	Sitagliptin	297	8.06 ± 0.8	-0.28 ± 0.1	<b>-0.35 (-0.53, -0.17)</b>	<.0001
<b>Add-on to background metformin +/- sulfonylurea</b>						
<b>112754 (52)</b>	Albiglutide	493	8.3 ± 0.9	-0.67 ± 0.04		
	Lantus	238	8.4 ± 1.0	-0.79 ± 0.06	<b>0.11 (-0.04, 0.27)</b>	0.0086
<b>112757 (52)</b>	Albiglutide	265	8.18	-0.55		
	Pioglitazone	268	8.28	-0.80	<b>0.25 (0.10, 0.40)</b>	0.2685
	Placebo	115	8.26	+0.33	<b>-0.87 (-1.07, 0.68)</b>	<.0001
<b>Add-on to background metformin +/- pioglitazone</b>						
<b>112755 (52)</b>	Albiglutide	149	8.10 ± 1.0	-0.81 ± 0.07		
	Placebo	149	8.13 ± 0.9	-0.05 ± 0.07	<b>-0.75 (-0.95, -0.56)</b>	<.0001
<b>Add-on to one or more (up to three) oral anti-diabetic agents (metformin, SU and TZDs)</b>						
<b>114179 (32)</b>	Albiglutide	398	8.18 ± 0.9	-0.78 ± 0.05		
	Liraglutide	402	8.15 ± 0.8	-0.99 ± 0.05	<b>0.21 (0.08, 0.34)</b>	0.0846
<b>Add-on therapy to basal insulin with or without oral anti-diabetic drugs</b>						
<b>108486 (26)</b>	Albiglutide	279	8.47 ± 0.9	-0.82 ± 0.06		
	Lispro	278	8.43 ± 0.9	-0.66 ± 0.06	<b>-0.16 (-0.32, 0.00)</b>	<.0001
<b>Special Population: Renal impaired +/- oral anti-diabetic drugs</b>						
<b>114130 (26)</b>	Albiglutide	242	8.08 ± 0.9	-0.83 ± 0.06		
	Sitagliptin	236	8.22 ± 0.9	-0.52 ± 0.06	<b>-0.32 (-0.49, -0.15)</b>	<.0001
<p>† LS mean change derived using an ANCOVA model with treatment, baseline HbA1c, prior MI, age and region included in the model. mITT population includes all randomized patients who received at least one dose of study medication and had at least one post-baseline HbA1c value. Last observation carried forward (LOCF) was used as the method to handle missing data. Data post onset of glycemic rescue therapy considered missing and imputed using LOCF.</p> <p>*Superiority p-values shown for placebo control comparisons. Non-inferiority p-values shown for active control comparisons. Highlighted values are comparisons which failed to exclude zero (statistically inferior) and failed to exclude the pre-specified non-inferiority margin of 0.3% (clinically worse).</p> <p># (Albiglutide 30 mg – PBO)</p> <p>§ (Albiglutide 50 mg – PBO)</p>						

The applicant has demonstrated that albiglutide improves glycemic control compared to placebo in the monotherapy setting and in combination with metformin, metformin and a sulfonylurea, and metformin and pioglitazone. In trial 112756 albiglutide 50 mg weekly was shown to provide nominally greater HbA1c reduction than albiglutide 30 mg weekly. The applicant has also demonstrated that albiglutide co-administered with optimized background anti-diabetic therapy is more efficacious than sitagliptin in two trials (at 26 and 104 weeks respectively), more efficacious than glimepiride in one trial (at 104 weeks), non-inferior to insulin glargine in one trial (at 52 weeks), non-inferior to insulin lispro in one trial (at 26 weeks), inferior to pioglitazone in one trial (at 52 weeks) and inferior to liraglutide in one trial (at 32 weeks).

An unusual feature of this program is that five of the eight trials evaluated primary efficacy at one year or more. In most other programs the primary efficacy endpoint is assessed at 6 months. In theory, this is desirable as it allows for an assessment of the glucose lowering response with chronic use. However, Dr. Rothman in his review notes that this approach resulted in a large amount of missing or imputed data at trial endpoint (in particular the week 104 end point) which undermines the reliability and confidence in the reported results. He also notes that the method selected to handle missing data (i.e., LOCF) may have introduced bias in the estimated results particularly in trials designed to demonstrate non-inferiority (e.g., early dropouts in non-inferiority trials handled using LOCF could bias toward the alternative).

I agree with Dr. Rothman in principles and believe that concerns regarding missing data impact mostly the accuracy of active-controlled comparisons. With regard to placebo-controlled comparisons, I am comforted by two observations. First, the majority of missing data was due to glycemic rescue and glycemic rescue was greatest in the placebo arms for all double-blind, placebo-controlled trials. Second, examination of the changes in HbA1c from baseline over trial visits show that glycemic improvements occurred at early time points (i.e., time points with less missing data) and that conclusions reached for early time points in placebo controlled trials would have been consistent with assessments performed at later time points (refer to Figure 2 in Dr. Mohamadi's review). In summary, missing data do not call into question the effectiveness of albiglutide compared to placebo at least in the short term (i.e., 26-weeks).

Responder analyses [i.e., proportion of trial participants reaching American Diabetes Association (ADA) target] and analyses based on fasting plasma glucose were consistent with primary analyses. As a key secondary endpoint in most trials the applicant evaluated weight changes from baseline across interventions. No difference in weight change from baseline was seen between albiglutide and placebo in trial 112756. The applicant has also shown that compare to a basal insulin, a prandial insulin and a sulfonylurea, use of albiglutide results in less weight gain for similar or better glycemic control.

The applicant performed a time-to-rescue analysis [REDACTED] (b) (4) in their 104 week trial (112753) as one of multiple secondary analyses in this trial. Time to glycemic rescue defined in this way is problematic because no accepted standard criteria for rescue exist and

determination regarding the need for rescue was left to investigators and not independently adjudicated. An analysis comparing the time to treatment failure (i.e., HbA1c > 7%) in responders between groups would have been more clinically relevant and robust.

## 8. Safety

Please refer to safety reviews by Drs. Vasisht, Bo Li and Avigan for full details of the safety findings in the albiglutide application. Dr. Mohamadi’s CDTL memorandum summarizes the key safety findings in the application. I agree with the reviewers that the analyses of safety in the albiglutide program do not raise concerns that would preclude approval of the product. Common adverse reactions included adverse reactions related to gastrointestinal reactions (e.g., diarrhea, nausea, vomiting), and injection site reactions (e.g., hematoma, erythema, rash, hypersensitivity). Gastrointestinal adverse reactions have been observed in currently marketed GLP-1 agonists and are mitigated through product labeling.

### *Size of the Database Used in Safety Analyses:*

For the review of overall safety Drs. Vasisht and Mohamadi focused on a pool of 7 phase III trials and their extensions. Studies in this pool include all studies described in Table 1 with the exception of the renal impairment study. These differed in design, size, albiglutide dose evaluated, duration and population enrolled (e.g., drug naïve, add-on to background therapy) and in aggregate constitute the greatest number of participants exposed and the longest exposure duration to albiglutide (See Table 2). Dr. Vasisht also presents data for a subset of patients within this pool of trials which is limited to data from the four pivotal efficacy trials containing a placebo arm.

**Table 2: Exposure in Main Safety Pool (Albiglutide versus All Comparators)**

<b>Subjects (N)</b>	
Albiglutide (30 and 50 mg) N	2116
Comparators (all)	2284
Placebo-only	923
<b>Total Exposure (Patient-Years)</b>	
Albiglutide (30 and 50 mg)	3370
Comparators (all)	3629
Placebo-only	841

In the pool of seven trials, 2116 participants received at least one dose of albiglutide (30 or 50 mg) for a mean duration of exposure to albiglutide of 75 weeks (i.e., 525 days). Total exposure to the 30 mg and 50 mg dose was similar (1720 versus 1650 patient years for the 30 and 50 mg dose). Demographic, anthropometric and disease characteristics were balanced between albiglutide and all comparators. The mean age of the population was 55 years and 1.5% of participants were older than

75 years of age. Fifty one percent of subjects were male; 48% were White, 15% were Black or African American and 9% were Asian. At baseline, participants had had diabetes for an average of 8 years. The mean HbA1c (SD) at baseline was 8.2%. Baseline renal function based on estimated GFR was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients.

*Deaths, Serious Adverse Events and Events Leading to Discontinuations:*

No imbalance in incident deaths was noted between patients treated with albiglutide (0.5 per 100 patient-years) and patients randomized to comparator (0.5 per 100 patient-years). Dr. Vasisht and Mohamadi reviewed narratives for all deaths in the program and conclude that clinical descriptions of the events in narratives do not raise concerns for a drug-related specific cause of death.

The proportion of nonfatal serious adverse events was similar in between albiglutide and comparators (11%) [Source integrated analysis of safety Table SP3-14.1.1]. More serious adverse events in the “Infections and infestations”, “Cardiac disorders”, and “Nervous systems”, systems organ classes were reported in albiglutide-treated patients than in comparator-treated patients. Dr. Vasisht and Mohamadi performed a causality assessment for serious adverse events which were seen more commonly in albiglutide treated patients [i.e., pneumonia (3 versus 12 for comparators versus placebo), appendicitis (0 versus 5 for comparators versus albiglutide), atrial fibrillation (2 versus 9 for comparators versus albiglutide), and pancreatitis (1 versus 3 for comparators versus albiglutide)]. Numerical imbalance in these events are small and narrative review revealed confounding by presence of underlying disease or risk factors (e.g., for atrial fibrillation underlying heart disease; for pneumonia underlying lung disease or precipitating event). Nevertheless, Drs. Vasisht and Mohamadi are of the opinion that there is sufficient evidence for product relatedness (i.e., strength of association, consistence of the finding across several trials, and biological plausibility) that these adverse reactions should be described in product label and followed prospectively in the large cardiovascular outcomes trial that will be required post-marketing. I concur with their assessments. Of note, the impact of a potential product-related increased risk of atrial fibrillation on major cardiovascular outcomes was formally and prospectively evaluated in the pre-market CV-risk assessment (refer to section on pre-market *Cardiovascular Risk Assessment* below).

The incidence of liver related adverse events was similar between albiglutide and all comparators. The largest imbalance not favoring albiglutide was observed for incident adverse events related to the investigations organ class and coded to the preferred term ‘GGT increased’ (0.9% vs. 1.5% for placebo versus albiglutide). The reason for the imbalance in ‘GGT increased’ is not clear but could suggest cholestasis plausibly related to the effect of GLP-1 on choledochal motility.

Two subjects randomized to albiglutide experienced significant liver injury accompanied by a concomitant rise in total bilirubin. One case occurred in a subject with acute Hepatitis B seroconversion and the other case was confounded by a history of recent international travel, concomitant medications (including naproxen), and the presence of gallstone disease diagnosed three

weeks after the events. Events of liver injury on albiglutide will be prospectively followed in the dedicated cardiovascular outcomes trial.

The risk of hypoglycemia with albiglutide is low with incident hypoglycemia rates similar between albiglutide and placebo. The risk of hypoglycemia increases when albiglutide is used in combination with a sulfonylurea or insulin. This will be shown in product label.

The proportion of patients who discontinued due to occurrence of an adverse event was higher in albiglutide-treated patients (5.7 versus 7.8% for comparators versus albiglutide). The imbalance in withdrawal was due to a greater proportion of patients withdrawing from the albiglutide arm due to injection site reactions (0.6 versus 2.1% for comparators versus albiglutide). A causal relationship to the drug is highly likely in light of the marked imbalance and route of administration.

### *Common Adverse Reactions*

Common adverse reactions seen more frequently on albiglutide than placebo and attributed to albiglutide use included events related to gastrointestinal complaints (i.e., diarrhea, nausea, vomiting, and dyspepsia) as well as events related to injection site reactions (hematoma, erythema and rash). Most injection site reactions (85%) were not associated with the presence of anti-albiglutide antibodies and most (73%) were judged as “mild” by investigators. More patients on albiglutide than on placebo<sup>6</sup>: discontinued due to an injection site reaction (2% versus 0.2%), experienced more than 2 reactions (38% versus 20%), had a reaction judged by investigators to be “moderate” or “severe” (27% versus 6%) and required local or systemic treatment for the reactions (36% versus 11%). Gastrointestinal and injection site reactions are described in detailed and featured prominently in the final negotiated product label. The current label limits the use of albiglutide in patients with pre-existing severe gastrointestinal disease (i.e., such as gastroparesis). Patients and prescribers will be informed that injection site reactions, sometimes severe, have been observed with albiglutide use and can take appropriate action to address this risk.

### ***Application Specific Concerns***

Thyroid C-cell tumors (including Medullary Thyroid Carcinoma), pancreatitis, hypersensitivity reactions, immunogenicity, pneumonia, atrial fibrillation/flutter and renal impairment in patients experiencing severe gastro-intestinal symptoms were identified as potential risks associated with albiglutide use. These risks have been reviewed in details in Drs. Vasisht and Mohamadi’s reviews.

Dr. Vasisht identified at least one serious hypersensitivity reaction (i.e., associated with systemic symptoms hypersensitivity reaction) that was likely product related (i.e., recurred with re-challenge). This serious risk will be presented in Section 5.4 of the label and albiglutide will be contra-indicated in patients who experience this product-related risk.

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<sup>6</sup> Note: Insulin was used as rescue therapy in placebo arm and analyses of adverse reactions include rescue medications.

Immunogenicity was reviewed by Drs. Pedras-Vasconcelos, Vasisht and Mohamadi. In the pool of 7 placebo and active controlled trials 5.5% of patients exposed to albiglutide developed anti-albiglutide antibodies. None of these anti-bodies were shown to neutralize albiglutide activity or endogenous GLP-1 activity. Presence [and dose (i.e., high titer)] of anti-albiglutide antibody was not found to correlate with lower efficacy or specific patterns of adverse reactions.

Renal impairment is a class related risk labeled across other members of the class. Renal impairment is believed to be secondary to the occurrence of gastrointestinal adverse reactions and consequent dehydration. In the dedicated renal study gastro-intestinal adverse reactions were observed to increase in frequency as renal function declined. This risk will be mitigated through product labeling.

Thyroid C-cell tumors and pancreatitis are class related concerns and are labeled as serious product related risks in marketed long-acting GLP-1 agonists. The potential risk of Thyroid C-cell tumors stems from observation of dose-related and treatment-duration dependent increases in the incidence of thyroid C-cell tumors (i.e., adenoma and carcinoma) in rodents exposed to long acting GLP-1 over a lifetime. It is unknown whether rodent studies are relevant to informing human risk. In the albiglutide program one case of medullary thyroid carcinoma was diagnosed in a patient exposed to albiglutide and one in a patient exposed to comparator. The case in the albiglutide arm, was exposed to albiglutide for 21 days, had undiagnosed MEN-2 (confirmed by RET proto-oncogene testing) and was found to have had an extremely elevated baseline calcitonin levels (480 pg/mL) signaling the presence of an underlying MTC that preceded albiglutide exposure. To mitigate the risk of Thyroid C-cell tumor, the risk will be featured in a Boxed Warning, the drug will not be indicated as first line therapy and will be contraindicated in patients at risk of developing MTC. The risk of pancreatitis will be communicated in the Warning and Precautions section of the product label and instructions to prescribers with regard to risk mitigation will be included. Both risks will be further mitigated using a Risk Evaluation and Mitigation Strategy which consists of a communication plan to inform health care providers of these serious risks.

*Cardiovascular Risk Assessment:*

Please refer to Dr. Bo Li's review for details. To assess whether albiglutide use is associated with an unacceptable increased in cardiovascular (CV) risk, the applicant performed a meta-analysis of clinical trials. This assessment of cardiovascular risk was prospective, pre-specified, reviewed by the Agency and carried out in accordance with the general principles laid out in the December 2008 FDA Guidance for Industry Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. The cardiovascular meta-analysis was based on data from nine completed randomized double-blind phase II and phase III trials (Studies GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP108486, GLP114130, GLP114179 and GLP110932).

The primary comparison for the meta-analysis was between all albiglutide doses and all comparators. The primary safety endpoint was MACE+, a composite endpoint comprising CV death, non-fatal

myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina. A key secondary endpoint was MACE, a composite endpoint comprising CV death, non-fatal MI, or non-fatal stroke. All events included in the meta-analysis were based on positively adjudicated events determined by a blinded Clinical Event Committee using accepted standardized event definitions. The pre-specified primary statistical analysis used a Cox proportional hazards model, stratified by trial.

MACE+ event rates in the albiglutide program were low (i.e., ~1% per year) and are in keeping with the fact that the applicant did not recruit particularly high CV-risk participants in glycemic efficacy trials. Results of the meta-analysis exclude the 1.8 pre-marketing CV-risk margin for MACE+ [Hazard ratio (97.55% CI) based on 91 incident events was 0.93 (0.55, 1.58)] and MACE-only [Hazard ratio (97.55% CI) based on 82 incident events was 0.97 (0.55, 1.69)]. Analyses of the individual components of MACE+ were consistent with overall conclusions (refer to figure 4 in Dr. Li's review). For full details of these analyses the reader is referred to Tables 6, 7 and 8 of Dr. Bo Li's review.

Dr. Li also performed subgroup analyses to explore CV-risk across baseline characteristics including: gender, race, age, geographic region, BMI, history of CV-disease, and duration of diabetes. Results of these analyses were generally consistent with results based on overall data.

## **9. Advisory Committee Meeting**

Albiglutide is the fourth member of the GLP-1 agonist class of anti-diabetic drugs. No new efficacy or safety issue identified in the application rose to the level of requiring the input from an advisory panel. Therefore no advisory committee was convened.

## **10. Pediatrics**

Please refer to Dr. Mohamadi's CDTL review for review of relevant pediatric issues.

## **11. Other Relevant Regulatory Issues**

There are no other unresolved relevant regulatory issues

## **12. Decision/Action/Risk Benefit Assessment**

- Regulatory Action

I recommend approval, pending agreement on final labeling.

- Risk Benefit Assessment

### Benefit

The applicant has demonstrated in adequate and well controlled trials that albiglutide doses of 30 and 50 mg administered subcutaneously once weekly result in clinically meaningful improvement glycemic control compared to placebo in patients with type 2 DM inadequately controlled with diet and exercise, metformin, metformin with or without a sulfonylurea and metformin with or without pioglitazone. The applicant has compared the effect of albiglutide to several active comparators across various treatment settings. In these comparisons, albiglutide co-administered with optimized background anti-diabetic therapy was shown to be more efficacious than sitagliptin in two trials (at 26 and 104 weeks respectively), more efficacious than glimepiride in one trial (at 104 weeks), non-inferior to insulin glargine in one trial (at 52 weeks), non-inferior to insulin lispro in one trial (at 26 weeks), inferior to pioglitazone in one trial (at 52 weeks) and inferior to liraglutide in one trial (at 32 weeks). Glucose lowering with albiglutide was weight neutral and was not associated with a high risk of hypoglycemia compared to placebo. In contrast, weight gain and hypoglycemia are well recognized adverse reactions associated with insulin and sulfonylurea use. Albiglutide is efficacious in patients with moderate renal impairment and carries a low inherent hypoglycemic risk compared to some available therapeutic options (i.e., sulfonylurea and insulin) for this important patient subgroup. In contrast to the majority of available anti-diabetic agents, albiglutide offers the convenience of a once weekly administration schedule.

### Risks

Glucose lowering with albiglutide is not associated with an inherently high risk of hypoglycemia. The risk of hypoglycemia increases when albiglutide is added to drugs known to cause hypoglycemia (e.g., sulfonylurea and insulin). Some of the potential drug-related risks identified in the application (Thyroid C-cell tumors, pancreatitis, renal impairment in patients experiencing severe gastrointestinal reactions) are real or potential risks associated with this class of glucose lowering agents and are currently mitigated through product labeling and REMS (i.e., REMS apply to Thyroid C-cell tumors and pancreatitis only). No data in the application suggest the presence of qualitative or quantitative differences for these risks when comparing albiglutide to other currently approved long-acting GLP-1 products. Other potential product-related adverse reactions identified were based on a small number of events, may have arisen due to chance and do not rise to such magnitude as to preclude approval. The imbalance in pneumonia and supraventricular tachycardia events will be labeled and followed prospectively in the cardiovascular outcomes trial. Characteristics of patients developing these events will be described if applicable so that prescribers can make an informed decision when contemplating use of the product in the individual patient. Common product related adverse reactions were consistent with the drug's pharmacological effect on intestinal motility (gastro-intestinal adverse reactions) or the route of administration (injection site reactions). The applicant's pre-marketing CV-risk analysis excludes an excess CV-risk of 1.8.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Albiglutide will be approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a communication plan to inform health care providers about the serious risks of thyroid C-cell tumors and pancreatitis.

- Recommendation for other Postmarketing Requirements and Commitments

The following post-marketing studies will be required under the Pediatric Research Equity Act (PREA) or Food and Drug Administration Amendments Act (FDAAA).

1. A clinical trial to evaluate dosing, efficacy, and safety in pediatric patients;
2. A medullary thyroid carcinoma case registry of at least 15 years duration to identify any increase in MTC incidence related to albiglutide;
3. A cardiovascular outcomes trial (CVOT) to evaluate the cardiovascular risk of albiglutide in patients with type 2 diabetes at high baseline risk of cardiovascular disease

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/s/  
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JEAN-MARC P GUETTIER  
04/14/2014