

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125431Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	April 15, 2014
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	125431
Applicant Name	GlaxoSmithKline
Proprietary / Established (USAN) Names	Tanzeum albiglutide
Dosage Forms / Strength	Lyophilized powder contained within single use prefilled pens administered subcutaneously as 30 or 50 mg once weekly
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
Action:	<i>Approval</i>

1. Introduction and Discussion

This will be a brief summary of the basis for the regulatory action regarding albiglutide and the reader should review the action package for more detail. Albiglutide is a new recombinant human glucagon-like peptide (GLP-1) fusion protein agonist developed to improve glycemic control (anti-diabetic therapy) by augmenting glucose-dependent insulin secretion from pancreatic beta-cells. Albiglutide consists of two copies of a 30-amino acid sequence of modified human GLP-1 genetically fused to human albumin.

GLP-1 is a peptide released from the gastrointestinal tract during meals which stimulates insulin release, reduces hepatic glucose production and slows gastric emptying. Endogenous GLP-1 has a short half-life of less than two minutes being degraded by dipeptidyl peptidase (DPP-4). GLP-1 agonist agents (Byetta/exenatide, Victoza/liraglutide, Bydureon/exenatide synthetic) have been developed that resist DPP-4 degradation and are used in the treatment of type 2 diabetes. All agents are subcutaneously administered with albiglutide joining Bydureon as a once weekly injection. Victoza is administered once daily and Byetta is administered twice daily.

All GLP-1 agents share common safety concerns and albiglutide is no different. These safety concerns 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 albiglutide is supported by an extensive database. I therefore recommend an Approval action.

Efficacy

Below are the pivotal Phase 3 trials reproduced from Dr. Mohamadi's review (Page 15-16):

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 / extended release) ≥1500 mg daily or MTD <1500 mg	1. Placebo 2. Albiglutide (30 mg weekly, no uptitration).	1:1 Placebo [155/115] Albiglutide 155/133]	Change from baseline HbA1c to week 52	104 weeks; double-blind; [156 weeks]

			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	MET, SU ⁴ and TZD either alone or in combination	1. Albiglutide (30 mg weekly with uptitration to 50 mg weekly at Week 6)	1:1 Albiglutide [422/346]	Change from baseline HbA1c to	None
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 alphaglucoisidase 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.

The primary endpoint was the change in HbA1c from baseline to the primary assessment time point (26, 32, 52 or 104 weeks). Secondary endpoints included change from baseline in HbA1c over time, change from baseline in fasting plasma glucose (FPG), proportion of

subjects achieving HbA1c treatment goal of <6.5% or <7.0%, time to hyperglycemia rescue and change from baseline in body weight.

The table below summarizes the primary efficacy results (Dr. Mohamadi's review, page 19):

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						
GLP112758 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 (-1.18, -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 52 weeks	Albiglutide	285	8.18 (0.908)	-0.55 (-0.65,- 0.44)		
	Pioglitazone	288	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 28 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)	-0.99 (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.

Compared to placebo, albiglutide provided a mean baseline reductions of HbA1c of -0.7% to -0.89% for 30 mg and 50 mg doses respectively. Mean differences from placebo were -0.84% and -1.04% for 30 mg and 50 mg doses respectively. Albiglutide has efficacy as add-on therapy to various agents and provided slightly greater efficacy when compared to sitagliptin and glimepiride but did not establish non-inferiority to pioglitazone or liraglutide. Secondary endpoints generally supported primary efficacy results. Subjects treated with albiglutide in general did not gain weight compared to other active agent comparisons and in particular compared to insulin and sulfonylurea.

These studies demonstrate that albiglutide is effective at improving glycemic control in Type 2 diabetic subjects under a variety of relevant clinical use conditions.

Safety

The major safety database was comprised of 4,400 subjects participated in the seven integrated Phase 3 trials, 2,116 exposed to albiglutide and 2,284 exposed to placebo or active comparators. The overall safety profile is similar to other members of the GLP-1 class. Some imbalances not recognized with other GLP-1 drugs were identified and are presented in the table below reproduced from Dr. Mohamadi’s review (page 30).

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.

Specifically, imbalances based on few events, were noted for appendicitis, pneumonia, as well as atrial fibrillation and the team has recommended that these go into labeling. It is always difficult to evaluate a potential safety signal based on few events. In this instance, we are fortunate that a large CVOT will help better define these signals going forward. Therefore, it is reasonable to be cautious in regard to warning about potential problems while we await further safety information.

The cardiovascular evaluation of albiglutide fulfilled criteria from the 2008 guidance that would allow marketing pending a post-marketing required cardiovascular outcome trial. This is demonstrated in the table below from Dr. Mohamadi's review (page 40-41).

Primary analysis results for MACE+ (CVE, on-study)

	Albiglutide	Comparator
	(N = 2524)	(N = 2583)
	[PY = 4214.7]	[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

As would be expected from an injectable peptide, albiglutide is immunogenic and 4.4% of subjects across the program developed albiglutide antibodies. Serious adverse event rates occurred at similar rates between antibody-positive and antibody-negative subjects receiving albiglutide. Injection site reactions occurred more frequently in the albiglutide treated group compared to placebo-treated subjects (17.6% vs. 7.5%). In albiglutide-treated subjects, severe reactions occurred 1.9% of the time compared to none in placebo-treated subjects.

Advisory Committee Meeting

An AC meeting was not held as albiglutide is not the first drug approved in its class, the safety profile is similar to that of other drugs in the GLP-1 class, the clinical study design is acceptable and evaluation of safety data did not raise significant safety or efficacy issues that were unexpected for a drug of this class in the intended population.

Conclusions and Recommendations

Albiglutide has demonstrated efficacy for the 30 mg and 50 mg doses administered once weekly with suggestions of dose ordering. The safety profile is similar to that of already approved GLP-1 products with the exception of some imbalances in adverse events based on limited numbers as noted above. Several PMRs are planned for further evaluation of these findings. Toward the end of the review cycle, FDA was made aware of a new process related impurity. The sponsor had already done extensive investigation before alerting the Agency. Upon review of additional documents provided, the CMC team believed that product quality and sterility would not be impacted and recommend approval.

I recommend approval of albiglutide.

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/s/

CURTIS J ROSEBRAUGH
04/15/2014