Efficacy and Safety of the Once-Weekly GLP-1 Receptor Agonist Albiglutide Versus Sitagliptin in Patients With Type 2 Diabetes and Renal Impairment: A Randomized Phase III Study

Lawrence A. Leiter,[1] Molly C. Carr,[2] Murray Stewart,[2] Angela Jones-Leone,[2] Rhona Scott,[3] Fred Yang,[2] and Yehuda Handelsman[4]

DOI: 10.2337/dc13-2855

OBJECTIVE

To evaluate weekly subcutaneous albiglutide versus daily sitagliptin in renally impaired patients with type 2 diabetes and inadequately controlled glycemia on a regimen of diet and exercise and/or oral antihyperglycemic medications.

RESEARCH DESIGN AND METHODS

In this Phase III, randomized, double-blind, multicenter, 52-week study, the primary study end point was HbA_{1c} change from baseline at week 26 in patients with renal impairment, as assessed with estimated glomerular filtration rate and categorized as mild, moderate, or severe (≥60 to ≤89, ≥30 to ≤59, and ≥15 to ≤29 mL/min/1.73 m^2, respectively). Secondary end points included fasting plasma glucose (FPG), weight, achievement of treatment targets, hyperglycemic rescue, and safety.

RESULTS

Baseline demographics were similar across treatment and renal impairment groups with overall mean age of 63.3 years, BMI of 30.4 kg/m^2, HbA_{1c} of 8.2% (66 mmol/mol), and diabetes disease duration of 11.2 years. HbA_{1c} change from baseline at week 26 was significantly greater for albiglutide than sitagliptin (−0.83% vs. −0.52%, $P = 0.0003$). Decreases in HbA_{1c}, FPG, and weight were seen through week 52. Time to hyperglycemic rescue through week 52 was significantly longer for albiglutide than sitagliptin ($P = 0.0017$). Results of safety assessments were similar between groups, and most adverse events (AEs) were mild or moderate. The incidences of gastrointestinal AEs for albiglutide and sitagliptin were as follows: overall, 31.7%, 25.2%; diarrhea, 10%, 6.5%; nausea, 4.8%, 3.3%; and vomiting, 1.6%, 1.2%, respectively.

CONCLUSIONS

Once-weekly albiglutide therapy in renally impaired patients with type 2 diabetes provided statistically superior glycemic improvement with almost similar tolerability compared with daily sitagliptin therapy.

[1]*Division of Endocrinology and Metabolism, Li Ka Shing Knowledge Institute and Keenan Research Centre for Biomedical Science, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada*
[2]*GlaxoSmithKline, King of Prussia, PA*
[3]*GlaxoSmithKline, Uxbridge, Middlesex, U.K.*
[4]*Metabolic Institute of America, Tarzana, CA*

Corresponding author: Lawrence A. Leiter, leiterl@smh.ca.

Received 5 December 2013 and accepted 23 June 2014.

Clinical trial reg. no. NCT01098539, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-2855/-/DC1.

The steady rise in the prevalence of type 2 diabetes worldwide has become a major health care issue due to associated increases in patient morbidity and mortality secondary to cardiovascular, renal, and neurological disease complications and the rising monetary and resource costs needed to manage these complications. Renal insufficiency is a common comorbidity in patients with type 2 diabetes, and the prevalence of chronic kidney disease (CKD) in patients with type 2 diabetes has been increasing (1), with the reported overall incidence of renal impairment in patients with type 2 diabetes ranging from 15 to 35% (based on estimated glomerular filtration rate [eGFR] $<$60 mL/min/1.73 m^2) (2–4).

Current treatment options for glycemic control are significantly limited for patients with type 2 diabetes and CKD (5,8–11), which often leads to the introduction of sulfonylurea and insulin therapy to maintain glycemic control. Further, therapeutic options for glycemic control can be associated with significant risks of hypoglycemia, weight gain, and fluid retention, which may add to the complexity of maintaining blood glucose, body weight, and blood pressure in this population (12–15).

Albiglutide, a novel, long-acting glucagon-like peptide-1 receptor (GLP-1R) agonist, was designed to retain the therapeutic actions of GLP-1 while having a greatly extended duration of action. Albiglutide was synthesized through genetic modification that resulted in the attachment of two modified recombinant human GLP-1 fragments linked in tandem to the amino terminus of the coding sequence for human albumin, and it retains GLP-1 glucose-dependent insulinotropic activities both in vitro and in vivo (16). With a half-life of approximately 5 days, the pharmacokinetic profile of albiglutide allow for once-weekly subcutaneous injections (16–20). To date, reported clinical studies, including a phase I study in patients with varying degrees of renal impairment (GLP108370), have shown albiglutide to be an effective, safe, and tolerable therapy when administered to patients with type 2 diabetes (16–21).

This study was conducted to compare the efficacy, safety, and tolerability of albiglutide given subcutaneously once weekly with sitagliptin given orally daily in patients with type 2 diabetes and renal impairment whose glycemia was inadequately controlled on their current regimen of either diet and exercise or specific antihyperglycemic therapy.

RESEARCH DESIGN AND METHODS

Study Design

This phase III, randomized, double-blind, active-controlled, two parallel-group, multicenter, 52-week study (Harmony 8) (GSK study number GLP114130) compared the efficacy and safety of once-weekly subcutaneous injections of albiglutide with that of daily oral sitagliptin in renally impaired patients with type 2 diabetes. Renal impairment was defined as mild (eGFR $\geq$60 to $\leq$89 mL/min/1.73 m^2), moderate (eGFR $\geq$30 to $\leq$59 mL/min/1.73 m^2), or severe (eGFR $\geq$15 to $\leq$29 mL/min/1.73 m^2) based on the MDRD formula (22). Albiglutide (30 mg) was given subcutaneously once weekly (with treatment-masked uptitration, if needed, to 50 mg weekly), and sitagliptin was dosed based on the eGFR value at randomization per the sitagliptin package insert. All patients continued to receive their prescribed oral antihyperglycemic medication regimen (metformin, thiazolidinedione, sulfonylurea, or any combination of these oral antihyperglycemic medications) for the duration of the study with the exception of patients with GFR $<$60 mL/min/1.73 m^2, who were washed off their background metformin. Instructions for downtitration of sulfonylureas were also provided to avoid hypoglycemia.

There were four specific study periods: prescreening and screening (~2 weeks), run-in (4 weeks), treatment period (52 weeks, including 26 weeks of initial treatment and evaluation for primary efficacy and safety followed by an additional 26 weeks of treatment for secondary efficacy and safety assessments), and posttreatment follow-up (8 weeks). Patient assessments during the treatment period varied between weekly and quarterly. Independent, blinded adjudication and review of all suspected cardiovascular events took place over the entire treatment period. An independent, blinded pancreatitis adjudication committee reviewed all reported adverse events (AEs) of pancreatitis, serious AEs (SAEs) identified through broad and narrow SMQ searches as related to pancreatitis, and other events identified by the pharmacovigilance group as related to pancreatitis, as well as amylase and/or lipase measurements (three or more times the upper limit of normal) regardless of suspected etiology, to determine whether adjudication for pancreatitis was warranted.

After randomization, patients who experienced persistent hyperglycemia qualified, on the basis of prespecified HbA_{1c} and/or fasting plasma glucose (FPG) values, to undergo masked dose titration followed by hyperglycemia rescue as needed (Supplementary Table 2). Given the blinded nature of the study, uptitration also occurred in the sitagliptin group, but the actual dose received did not change. Patients continued to receive study medication in a blinded fashion after rescue.

The primary end point of the study was to evaluate the efficacy of albiglutide compared with that of sitagliptin on the change in HbA_{1c} from baseline at week 26. Secondary end points over time included HbA_{1c}, FPG, body weight, proportion of patients who met prespecified HbA_{1c} treatment targets, time to hyperglycemic rescue, and population pharmacokinetics of albiglutide. Pharmacokinetics are not reported here, as a population model that combined data from this and three other Phase III studies will be reported separately (23). Safety end points over time included evaluations of AEs and SAEs, safety events of special interest, clinical laboratory parameters, vital sign measurements, electrocardiogram readings, and physical examinations. Immunogenicity was also evaluated. There were no changes to the statistical plan, which was finalized before the database was frozen and treatment codes were unblinded.

This study was conducted in accordance with International Committee on Harmonisation Good Clinical Practices and the Declaration of Helsinki, and all patients provided written informed consent before they participated in this study.

Patients

Male and nonpregnant, nonlactating female patients $\geq$18 years of age with historical diagnoses of type 2 diabetes were enrolled. Patients were required to have baseline HbA_{1c} between 7.0 and 10.0% (53–86 mmol/mol), BMI between 20 and

45 kg/m^2, fasting C-peptide level of ≥0.8 ng/mL (0.26 nmol/L), GFR of ≥15 to <90 mL/min/1.73 m^2, hemoglobin of ≥10 g/dL for male patients and ≥9 g/dL for female patients, and normal levels of thyroid-stimulating hormone or clinically euthyroid.

Patients with malignant disease (except squamous cell or basal cell carcinoma) were excluded from the study. Further exclusion criteria included a history of diabetic gastroparesis, current ongoing symptomatic biliary disease or history of pancreatitis, significant gastrointestinal (GI) surgery or surgeries thought to significantly affect upper GI function, recent (within predefined time scales) clinically significant cardiovascular and/or cerebrovascular disease, a history of human immunodeficiency virus infection, and acute symptomatic hepatitis B or C infection. Patients who met additional exclusion criteria, including requirements for levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, amylase, lipase, or fasting triglycerides, were also excluded.

Randomization and Blinding

Approximately 500 patients were planned to be randomly assigned in a ratio of 1:1 to receive albiglutide plus sitagliptin matching placebo or albiglutide matching placebo plus sitagliptin. Eligible patients were stratified according to severity of renal impairment (mild, moderate, or severe), prior history of myocardial infarction (yes or no), and age (<65 or ≥65 years of age). An interactive voice response system was used for the blinded randomization, which was based on a sequestered fixed randomization schedule. Albiglutide/matching placebo was supplied as a fixed-dose (30 or 50 mg) pen injector system, which was injected subcutaneously into the abdomen. Sitagliptin (100 mg for patients with eGFR ≥50–89 mL/min/1.73 m^2, 50 mg for those with eGFR ≥30 to <50 mL/min/1.73 m^2, and 25 mg for those with eGFR <30 mL/min/1.73 m^2) and matching placebo were provided as overcoated tablets or capsules. No dose adjustments were made for degrees of renal impairment after randomization. Treatment compliance was assessed for both treatment groups through the return of unused study medication.

Sample Size and Statistical Analyses

Based on an expected treatment effect of 0% and an SD of 1.2%, the test of albiglutide versus sitagliptin had at least 91% power according to a one-sided, two-sample *t* test and a test-wise significance level of 0.025, with 200 completed patients per treatment group for a noninferiority margin of 0.4. With the significance on the noninferiority hypothesis, the superiority hypothesis had at least 90% power to reject the null hypothesis if the actual albiglutide superiority was 0.35% with a two-sided, two-sample *t* test and a test-wise significance level of 0.05. Allowing for as great as 20% early withdrawal, loss to glycemic follow-up, and rescue, we randomized 250 patients to each treatment group.

The primary analysis of the change in HbA_{1c} from baseline response at week 26 was applied to the intent-to-treat population using an ANCOVA model with main effects for treatment group, region, renal impairment severity, history of prior myocardial infarction, and age category as factors and baseline HbA_{1c} as a continuous covariate. Treatment-effect estimates (and associated hypothesis tests) of albiglutide were evaluated within this ANCOVA model as least squares (LS) means contrasts relative to sitagliptin. Patients who qualified for hyperglycemia rescue had their primary end point value for change in HbA_{1c} from baseline recorded at the time of rescue. Follow-up assessments continued beyond rescue. For patients who withdrew consent, were lost to follow-up, or otherwise discontinued participation, the last observation carried forward (LOCF) method was used for the primary analysis of HbA_{1c}. The ANCOVA analyses were also performed on HbA_{1c} change from baseline by visit up to week 52 with the observed case (OC) algorithm, which only included patients with data at the specified analysis time point and excluded data carried forward from earlier observations as was done under the LOCF procedure. For this report, LOCF analyses that excluded posthyperglycemic rescue values were used for the week 26 data and OC analyses that excluded posthyperglycemic rescue values were used for the week 52 data unless otherwise stated.

The other continuous secondary efficacy end points were analyzed in a fashion similar to that used for the primary end point. Fifty-two week efficacy was evaluated using time to hyperglycemia rescue and the proportion of patients who received hyperglycemia rescue. The safety analyses included comparative summaries of vital sign measurements, laboratory values, physical examination assessments, electrocardiogram readings, and on-therapy AE incidence rates, with events "on therapy" defined as events that occurred within 56 days of treatment regardless of rescue.

All analyses were conducted with SAS software (SAS Institute, Cary, NC), version 9.1 or higher.

RESULTS

Patients

This study was conducted at 134 centers in 15 countries between 7 May 2010 and 30 May 2012. A total of 771 patients were assessed for eligibility, and 507 patients were randomly assigned to receive albiglutide (*n* = 254) or sitagliptin (*n* = 253) (Supplementary Fig. 1). At least 97% of patients in each group received one or more doses of study medication. Overall dropout rates by week 52 were ~ 20% in the albiglutide group and 25% in the sitagliptin group.

Patient demographic and baseline characteristics were similar between the albiglutide and sitagliptin treatment groups. Of the assessed characteristics, only HbA_{1c} category showed a statistically significant difference between groups ($P < 0.05$); however, this difference was not considered to be clinically relevant and was likely due to the higher mean HbA_{1c} at baseline in the sitagliptin group (Table 1). Overall, ~52%, 41%, and 7% of patients had mild, moderate, or severe renal impairment, respectively.

Approximately 57% of patients (141 of 249) on albiglutide required dose uptitration to 50 mg, with 35% undergoing uptitration by week 26 and an additional 22.1% by week 48. The mean albiglutide dose was 40.2 mg at week 26 and 42.4 mg at week 52. The proportion of albiglutide-treated patients who required uptitration from 30 mg weekly to 50 mg weekly was similar among the mild (53% [69 of 128 patients]), moderate (60% [61 of 102 patients]), and severe (58% [11 of 19 patients]) renal impairment subgroups.

Treatment compliance was 98% for albiglutide and 93% for sitagliptin. Compliance rates <80% were lower in the albiglutide (1.6%) and matching placebo

Table 1—Patient demographics and baseline characteristics by treatment group (safety population)

	Albiglutide	Sitagliptin	Total	*P**
N	249	246	495	
Severity of renal impairment, *n* (%)				0.9522
Mild	128 (51.4)	128 (52.0)	256 (51.7)	
Moderate	102 (41.0)	101 (41.1)	203 (41.0)	
Severe	19 (7.6)	17 (6.9)	36 (7.3)	
Age (years), mean (SD)	63.2 (8.37)	63.5 (9.02)	63.3 (8.69)	0.733
<65 years	141 (56.6)	138 (56.1)	279 (56.4)	0.906
≥65 years	108 (43.4)	108 (43.9)	216 (43.6)	
Sex, *n* (%)				0.692
Female	113 (45.4)	116 (47.2)	229 (46.3)	
Male	136 (54.6)	130 (52.8)	266 (53.7)	
Race, *n* (%)†				
Black	36 (14.5)	42 (17.1)	78 (15.8)	
Asian	84 (33.7)	76 (30.9)	160 (32.3)	
White	113 (45.4)	114 (46.3)	227 (45.8)	
Other	17 (6.8)	16 (6.5)	33 (6.7)	
Diabetes duration (years), mean (SD)	10.83 (7.403)	11.62 (8.476)	11.23 (7.956)	0.271
Mean Baseline HbA_{1c}, mean (SD)	8.13 (1.036)	8.23 (0.942)	8.18 (0.991)	0.247
<8.0% (<63.9 mmol/mol)	131 (52.6)	107 (43.5)	238 (48.1)	0.042
≥8.0% (≥ 63.9 mmol/mol)	118 (47.4)	139 (56.5)	257 (51.9)	
Prior myocardial infarction, *n* (%)				0.841
Yes	21 (8.4)	22 (8.9)	43 (8.7)	
No	228 (91.6)	224 (91.1)	452 (91.3)	
Body weight (kg), mean (SD)	83.25 (19.902)	82.84 (20.649)	83.04 (20.275)	0.821
BMI (kg/m^2), mean (SD)	30.35 (5.466)	30.43 (5.828)	30.39 (5.644)	0.873
Baseline vital signs, mean (SD)				
Systolic blood pressure (mmHg)	132.9 (14.78)	132.8 (14.94)	132.9 (14.87)	0.940
Diastolic blood pressure (mmHg)	78.5 (10.34)	78.8 (9.17)	78.6 (9.79)	0.733
Baseline lipids, mean (SD)				
Total cholesterol (mmol/L)	4.7 (1.21)	4.5 (1.08)	4.6 (1.15)	0.053
HDL (mmol/L)	1.2 (0.32)	1.2 (0.32)	1.2 (0.32)	1.000
LDL (mmol/L)	2.5 (0.95)	2.4 (0.95)	2.5 (0.95)	0.245
Triglycerides (mmol/L)	2.3 (1.64)	2.0 (0.97)	2.2 (1.36)	0.014
Patients with any diabetes, *n* (%) condition^				
Dyslipidemia	177 (71.1)	172 (69.9)	349 (70.5)	0.776
Nephropathy	66 (26.5)	61 (24.8)	127 (25.7)	0.663
Peripheral neuropathy	62 (24.9)	58 (23.6)	120 (24.2)	0.731
Diabetic retinopathy	40 (16.1)	49 (19.9)	89 (18.0)	0.264

*The *P* value was for testing the null hypothesis that the population values (mean or proportion) were equal between the two treatment groups (albiglutide and sitagliptin). All tests were two sided. †Patients could be counted in more than one race category. A *P* value was not calculated for race. ^Diabetes conditions were not predefined in the protocol but were investigator assessed.

(1.6%) groups compared with the sitagliptin (11.4%) and matching placebo (14.8%) groups.

Efficacy

HbA_{1c} Change From Baseline at Primary End Point and Over Time

The model-adjusted LS mean for the primary end point of change from baseline in HbA_{1c} at week 26 was −0.83% (−9.1 mmol/mol) in the albiglutide group and −0.52% (−5.7 mmol/mol) in the sitagliptin group (Fig. 1*A*), with similar results across all three baseline eGFR groups (data not shown). The treatment difference (albiglutide vs. sitagliptin) was −0.32% (95% CI −0.49, −0.15) (−3.5 mmol/mol [95% CI −5.4, −1.6). The upper bound of the CI was below the prespecified noninferiority margin of 0.4% (4.4 mmol/mol), indicating noninferiority of albiglutide to sitagliptin. A superiority test conducted in accordance with a prespecified, step-wise procedure indicated that albiglutide was statistically superior to sitagliptin (*P* = 0.0003). The treatment effect of albiglutide seen at week 26 was maintained through week 52 (Supplementary Fig. 2*A*).

FPG

The change in FPG from baseline at week 26 was −1.42 mmol/L in the albiglutide group and −0.22 mmol/L in the sitagliptin group (Fig. 1*B*). At week 26, the difference in LS means (albiglutide vs. sitagliptin) was −1.20 mmol/L (*P* < 0.0001). Both treatment groups maintained decreases in FPG through week 52, with the mean change from baseline in FPG showing greater reductions for albiglutide than for sitagliptin at each time point through week 52 (Supplementary Fig 2*B*). At week 52, both albiglutide and sitagliptin demonstrated sustained glycemic effects (Supplementary Fig. 2*B*).

Clinically Meaningful HbA_{1c} Response

A higher percentage of patients in the albiglutide treatment group achieved the treatment targets of HbA_{1c} <6.5% (<48 mmol/mol) and <7.0% (<53 mmol/mol) at week 26 (albiglutide 15.3% and 42.6%, respectively, compared with sitagliptin 12.3% and 30.5%, respectively). The treatment difference between albiglutide and sitagliptin was statistically significant (*P* = 0.0077) for the treatment target of HbA_{1c} <7.0% (<53 mmol/mol) at week 26. The proportion of patients who reached the treatment targets of improvement in HbA_{1c} by at least 1.0% (10.9 mmol/mol), 1.5% (16.4 mmol/mol), or 2.0% (21.9 mmol/mol) by week 26 was higher in the albiglutide group than in the sitagliptin group. The differences were not significant at week 52.

Time to Hyperglycemia Rescue

There was a statistically significant difference between albiglutide and sitagliptin (*P* = 0.0017) in the mean time to hyperglycemia rescue through week 52. The proportion of patients who had required hyperglycemia rescue was lower in the albiglutide group than in the sitagliptin group at week 26 (6.1% [15 patients] vs. 12.1% [29 patients]) and at week 52 (17.9% [44 patients] vs. 28.3% [68 patients]). The probability of rescue at the end of 52 weeks was 20% for albiglutide and 34% for sitagliptin. Metformin was

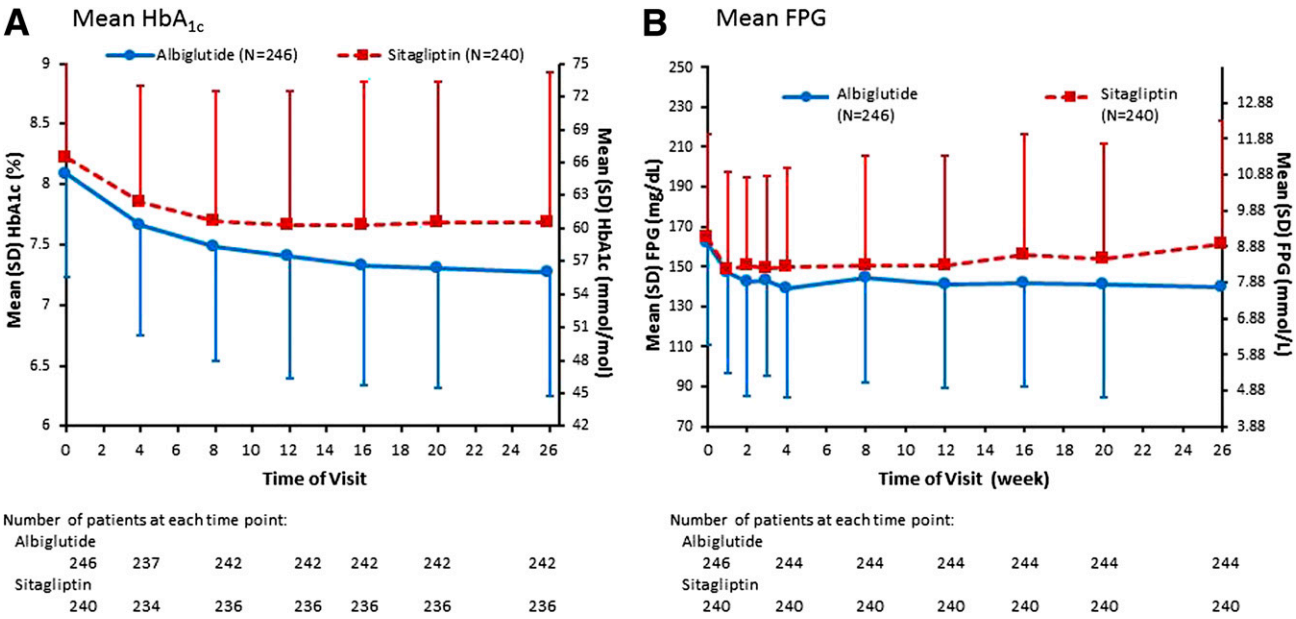

Figure 1—Summary of efficacy data through week 26 in the safety population using an LOCF analysis. Note: efficacy data through week 52 can be found in Supplementary Fig. 2. (A high-quality color representation of this figure is available in the online issue.)

the most commonly used rescue medication in both treatment groups.

Change in Body Weight

Patients in both treatment groups showed a modest mean loss in body weight through week 26, with a model-adjusted LS mean weight change from baseline of −0.79 kg for albiglutide and −0.19 kg for sitagliptin ($P < 0.05$). Weight loss from baseline was maintained through week 52 in the albiglutide group, whereas a small gain in mean body weight was observed in the sitagliptin group over this period (−0.82 kg and 0.32 kg, respectively; $P < 0.05$ [excluding postrescue values]).

Safety

AEs

The incidence of any AE and the event rates of on-therapy AEs over the course of the study were similar between the two treatment groups (83.5% and 347 AEs/100 person-years with albiglutide and 83.3% and 331 AEs/100 person-years with sitagliptin). A summary of study AEs is presented in Table 2. Notably, there was no marked difference between the albiglutide and sitagliptin treatment groups in nausea events (4.8% vs. 3.3%) or vomiting events (1.6% vs. 1.2%) (Fig. 2). In both groups, most AEs were mild or moderate in intensity, and a similar proportion of patients in each group experienced severe AEs (13.7% with albiglutide and 14.6% with sitagliptin). On-therapy GI AEs occurred in 31.7% of albiglutide-treated patients (52.8 AEs/100 person-years) and in 25.2% of sitagliptin-treated patients (47.4 AEs/100 person-years). Diarrhea was the most commonly reported GI AE in both the albiglutide (10.0%) and sitagliptin (6.5%) groups. Other AEs prospectively defined as being of special interest included hypoglycemic events, injection-site reactions, potential systemic allergic reactions, pancreatitis, and thyroid cancer (Table 2). A higher proportion of patients in the albiglutide group (24.1%) than in the sitagliptin group (15.9%) experienced a hypoglycemic event, with few events occurring in patients who were not receiving sulfonylurea. One case (0.4%) of severe hypoglycemia was reported with albiglutide, and four cases (1.6%) were reported with sitagliptin. Higher proportions of patients in the albiglutide group than in the sitagliptin group experienced injection site reactions (8.0% vs. 3.7%, respectively) and AEs that the investigator assessed as related to study medication (21.7% vs. 13.8%, respectively). The proportion of patients who withdrew due to AEs was 10.4% in the albiglutide group and 10.6% in the sitagliptin group. Renal failure, renal impairment, and hyperglycemia were the only events that led to withdrawal reported by more than more patient in either treatment group.

SAEs

Fatal and nonfatal SAEs were similar between the albiglutide group (32 patients [12.9%]) and the sitagliptin group (36 patients [14.6%]). With the exception of atrial fibrillation (reported for four patients on albiglutide and one patient on sitagliptin), the majority of SAEs were reported for no more than two patients in each treatment group. In both groups, SAEs in the "cardiac disorders and infections and infestations" system organ class were the most commonly reported.

A total of eight deaths occurred during this study: four on albiglutide (pleural mesothelioma, pancreatic pseudocyst, sudden cardiac death, and cardiac disorder) and four on sitagliptin (ischemic stroke, subarachnoid hemorrhage, malignant melanoma, and gastroenteritis). One patient in the albiglutide group was found incidentally (on computed tomography scan during work-up of hematuria) to have two pancreatic cysts and developed pancreatitis after a pancreatic fine needle aspirate. The patient went on to develop pancreatic pseudocyst and subsequently died; the blinded adjudication committee considered the event not related to treatment.

Other Safety Parameters

Measurements of hematology, serum chemistry, vital signs, electrocardiogram readings, and physical examinations were generally unremarkable.

Table 2—Patient safety through week 52 (safety population)

	Albiglutide	Sitagliptin
N	249	246
Overall AE incidence, *n* (%)		
Any AE	208 (83.5)	205 (83.3)
Fatal AEs	4 (1.6)	4 (1.6)
SAEs	32 (12.9)	36 (14.6)
Drug-related AEs	54 (21.7)	34 (13.8)
AEs leading to withdrawal of active treatment	26 (10.4)	26 (10.6)
Most common AEs, *n* (%)*		
Urinary tract infection	23 (9.2)	20 (8.1)
Diarrhea	25 (10.0)	16 (6.5)
Upper–respiratory tract infection	14 (5.6)	23 (9.3)
Nasopharyngitis	14 (5.6)	20 (8.1)
Hypertension	14 (5.6)	19 (7.7)
Anemia	16 (6.4)	10 (4.1)
Peripheral edema	14 (5.6)	8 (3.3)
Constipation	15 (6.0)	6 (2.4)
GI disorders system organ class, *n* (%)		
Any event	79 (31.7)	62 (25.2)
Nausea	12 (4.8)	8 (3.3)
Vomiting	4 (1.6)	3 (1.2)
Hypoglycemic events, *n* (%)		
Any hypoglycemic event	60 (24.1)	39 (15.9)
With background sulfonylurea	56 (22.5)	35 (14.2)
Without background sulfonylurea	4 (1.6)	4 (1.6)
Documented symptomatic	29 (11.6)	15 (6.1)
Severe	1 (0.4)	4 (1.6)
ISRs, *n* (%)		
Any	20 (8.0)	9 (3.7)
1–2	15 (75.0)	9 (100.0)
Total number of events	88	11
Deemed mild	70 (79.5)	10 (90.9)
ISR-related study withdrawals	0	0
Potential systemic allergic reactions, *n* (%)†		
Angioedema	1 (0.4)	1 (0.4)
Anaphylaxis	0	0
Exfoliative rash	0	1 (0.4)
Lip swelling	1 (0.4)	0
Face edema	1 (0.4)	0
Pancreatitis, *n* (%)^	1 (0.4)	0
Thyroid cancer, *n* (%)	0	0

ISR, injection site reaction. *Occurred in ≥5% of patients in either treatment group. †Potential allergic reactions were identified through a standard MedDRA query. ^Preferred term of pancreatic pseudocyst.

Shifts from baseline in renal impairment category, as assessed with eGFR, were similar between groups, with no clearly identifiable treatment-associated trends evident in either serum creatinine or the ratio of urine albumin to creatinine.

Immunogenicity

The incidence of anti-albiglutide antibodies was 3.0% (7 of 231 patients) in the albiglutide group, including 1 patient (0.4%) with preexisting antibodies at baseline. All antibodies detected were of low titer and nonneutralizing. Of the seven anti-albiglutide antibody–positive patients, five tested positive for anti–GLP-1 antibodies and one tested positive for anti-albumin (anti–human serum albumin) antibodies. No reactivity with glucagon was observed. One patient in the albiglutide arm experienced a nonserious event of angioedema (local, nonsystemic, lower lip), and one patient in the sitagliptin arm experienced a serious event of angioedema (thought to be attributable to iodine). Both patients remained in the study. No SAEs or potential systemic allergic reactions were observed in the patient with anti-albiglutide antibodies.

CONCLUSIONS

This study demonstrated that once-weekly albiglutide therapy effectively and safely lowers blood glucose concentrations in patients with type 2 diabetes and varying degrees of renal impairment. The primary study end point of change from baseline in HbA_{1c} demonstrated the noninferiority of albiglutide to sitagliptin. Furthermore, albiglutide was shown to be statistically superior to sitagliptin in lowering HbA_{1c} at week 26. Nearly 60% of the patients treated with albiglutide achieved HbA_{1c} levels $<$7% by week 26. However, it should be noted that more patients in the albiglutide group than in the sitagliptin group had HbA_{1c} levels $<$8% at baseline. Similarly, a rapid albiglutide treatment effect was also seen with FPG, where there was a steep decline from baseline through week 4 that was maintained through week 26. These data are further supported by the sustained effect, as evidenced by the lower proportion of patients who required hyperglycemia rescue in the albiglutide group compared with the sitagliptin group.

Recent treatment guidelines have positioned incretin-based therapies, including GLP-1R agonists, as prominent therapy options due to their substantial effectiveness in improving glycemic control and other positive attributes such as modest weight loss, low rates of hypoglycemia, and potential for improved β-cell mass/function and possible cardiovascular protective actions (24). Further, these guidelines indicate that GLP-1R agonists that do not depend on renal function for clearance may be an appropriate alternative for some patients when metformin use is not an option.

With few exceptions, albiglutide and sitagliptin in this study had similar safety profiles, including for events of special interest. Although the relatively limited number of patients with severe renal impairment did experience higher frequencies of GI events compared with patients with mild and moderate renal impairment, there were no new safety concerns identified for albiglutide in this study than were included in similar previous clinical trials (16–21). Diarrhea (the most common GI event in both treatment groups) and constipation were seen at modestly higher incidences in patients treated with albiglutide than in those treated with sitagliptin; however, there was no marked difference in nausea or vomiting events in either treatment group. Furthermore, uptitration of albiglutide did not increase

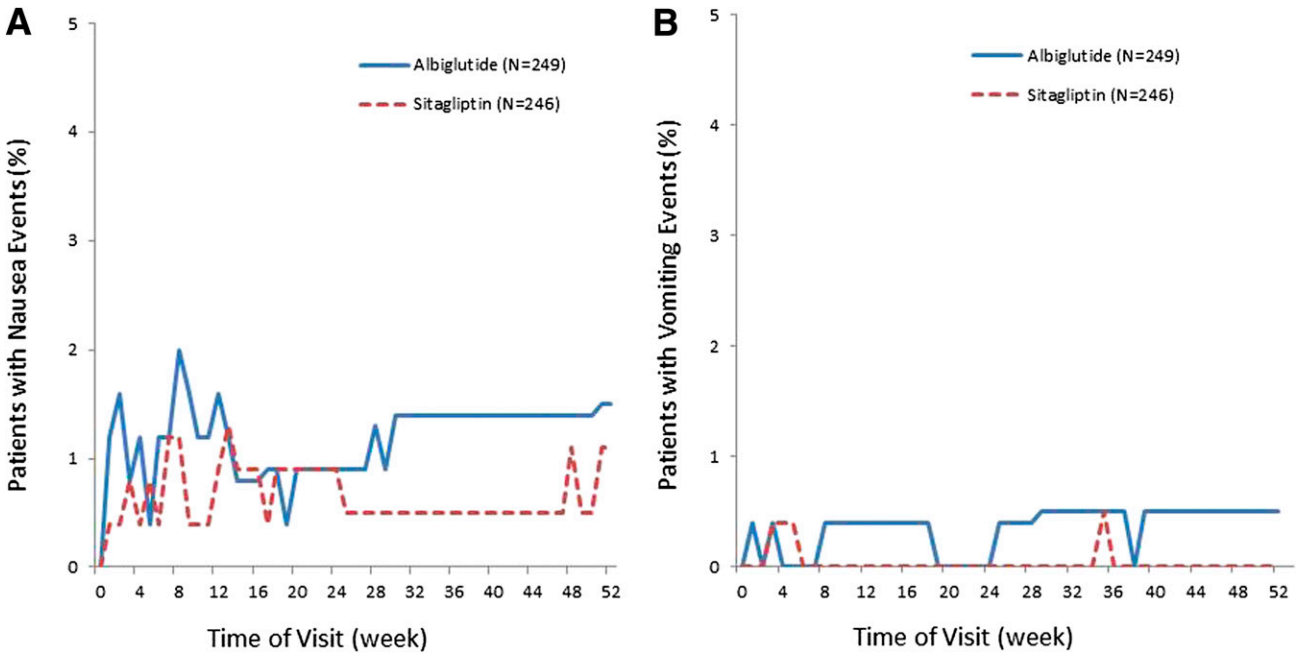

Figure 2—Nausea (*A*) and vomiting (*B*) through week 52 in the safety population. (A high-quality color representation of this figure is available in the online issue.)

the number of reported GI events, and very few GI events led to withdrawal.

These data should be considered in the context of three unique design features in this study. First, patients with varying degrees of renal impairment were enrolled in this study. Given that many medications used to treat type 2 diabetes require dose reduction based on renal dysfunction for optimal therapeutic benefit, it is important to evaluate albiglutide in the context of this patient population. However, as a large therapeutic protein that is degraded by enzymatic catabolism to its constituent amino acids, albiglutide should not require renal elimination or any dose adjustment that is based on degree of renal impairment, as supported by a previous albiglutide study in patients with varying degrees of renal impairment (GLP108370). This unique aspect of albiglutide could prove more convenient for this challenging population, potentially improving patient medication compliance and treatment efficacy. A second unique feature of the study design was that uptitration of the blinded study drug was need based when prespecified glycemic thresholds were met, with no preestablished or standardized time point for dose uptitration. Thus, the efficacy and safety data for albiglutide were combined for the 30-mg and 50-mg albiglutide doses. In contrast, sitagliptin dosing was determined according to each patient's renal impairment status at baseline, as outlined in the sitagliptin prescribing information. Finally, the use of rescue medication was embedded in the treatment program to facilitate patients remaining in the study on blinded study medication through week 52, which enabled the collection of additional safety and efficacy data. While the primary efficacy assessments were independent of rescue medication, the main safety assessments included all available patient information regardless of rescue status.

This study supports the potential advantages of albiglutide treatment in patients with type 2 diabetes who have inadequate glycemic control and any degree of renal insufficiency without the need for dose adjustment.

There were several potential limitations in this study. First, there were only 19 patients with severe CKD who were treated with albiglutide (and 17 sitagliptin patients). Owing to the small sample size and the potential for variable drug responses in this population, these results for patients with severe CKD cannot be considered definitive. A second limitation was that fewer patients completed 52 weeks of treatment (198 on albiglutide and 178 on sitagliptin) than completed week 26 (220 on albiglutide and 206 on sitagliptin), which limits the interpretation of the longitudinal sustainability response. Finally, HbA_{1c} may be a less reliable measure of efficacy in patients with renal impairment; however, both treatment groups had similar degrees of renal impairment, so the effect should not bias the interpretation of the results.

These study data from patients with CKD suggest a positive benefit-to-risk evaluation for the use of 30 or 50 mg albiglutide to reduce blood glucose levels in patients with type 2 diabetes and any degree of renal impairment, thus potentially filling a current unmet need. Results from additional phase III studies that are currently underway as part of the albiglutide clinical development program are consistent with the present efficacy and long-term safety findings from Harmony 8 (25–29).

In conclusion, albiglutide had a favorable benefit-to-risk profile and was generally well tolerated in patients with type 2 diabetes and mild, moderate, or severe renal impairment. In contrast to reports on postmarketing experience with currently approved GLP-1R agonists, albiglutide therapy was not associated with worse tolerability than that observed in other populations. In the

present comparison with sitagliptin, albiglutide produced statistically superior glycemic improvement and did not require dose adjustment specific to renal impairment. Given the various restrictions imposed on other antihyperglycemic therapies in this population, albiglutide may be another treatment option for patients with type 2 diabetes and renal impairment.

Duality of Interest. This study was sponsored by GlaxoSmithKline. The authors thank the following employees of GlaxoSmithKline for their specific contributions: Caroline Perry, PhD, for study management support and Douglas L. Wicks, MPH, CMPP, for management of manuscript development. The authors acknowledge the editorial support provided by Amy Myers, MPH, PPD, Inc. (production of draft outline, production of manuscript, assembly of tables and figures), and Christopher Barnes, PhD, PPD, Inc. (production of manuscript), which was funded by GlaxoSmithKline. L.A.L. has received research funding from, has provided continuing medical education on behalf of, and/or has acted as a consultant to AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, Sanofi, Servier, and Takeda. M.C.C., M.S., A.J.-L., R.S., and F.Y. are employed by and shareholders of GlaxoSmithKline. M.S. and F.Y. have been issued a patent for GLP-1s in renal disease. Y.H. has received research funding from, has provided continuing medical education on behalf of, and/or has acted as a consultant to Amarin, Amgen Amylin, Boehringer Ingelheim, Bristol-Myers Squibb, diaDeux, DSI, Eisai, Gilead, Intarcia, GlaxoSmithKline, Halozyme, Janssen, Lexicon, LipoScience, Merck, Novo Nordisk, Sanofi, Santarus, Takeda, and Vivus. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. L.A.L., M.C.C., M.S., A.J.-L., R.S., F.Y., and Y.H. contributed to study design, conduct, or data collection; performed data analysis or interpretation; and contributed to writing, reviewing, revising, and approving the manuscript for submission. L.A.L. and Y.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 73rd Scientific Sessions of the American Diabetes Association, Chicago, IL, 21–25 June 2013, and at the 49th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain, 23–27 September 2013.

References

1. Koro CE, Lee BH, Bowlin SJ. Antidiabetic medication use and prevalence of chronic kidney disease among patients with type 2 diabetes mellitus in the United States. Clin Ther 2009; 31:2608–2617
2. Dreyer G, Hull S, Aitken Z, Chesser A, Yaqoob MM. The effect of ethnicity on the prevalence of diabetes and associated chronic kidney disease. QJM 2009;102:261–269
3. Middleton RJ, Foley RN, Hegarty J, et al. The unrecognized prevalence of chronic kidney disease in diabetes. Nephrol Dial Transplant 2006; 21:88–92
4. New JP, Middleton RJ, Klebe B, et al. Assessing the prevalence, monitoring and management of chronic kidney disease in patients with diabetes compared with those without diabetes in general practice. Diabet Med 2007;24:364–369
5. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement—executive summary. Endocr Pract 2013;19:536–557
6. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA 2010;303:1410–1418
7. Pioglitazone package insert [Internet], 2011. Deerfield, IL, Takeda Pharmaceuticals America, Inc. Available from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=search.drugdetails. Accessed 15 August 2013
8. Kahn SE, Haffner SM, Heise MA, et al.; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–2443
9. Byetta US package insert [Internet], 2011. San Diego, CA, Amylin Pharmaceuticals. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021773s029s030lbl.pdf. Accessed 21 October 2013
10. Victoza US package insert [Internet], 2012. Princeton, NJ, Novo Nordisk. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022341s007s009s013lbl.pdf. Accessed 21 October 2013
11. Januvia US package insert [Internet], 2012. Whitehouse Station, NJ, Merck & Co. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021995s023lbl.pdf. Accessed 21 October 2013
12. Ampudia-Blasco FJ, Rossetti P, Ascaso JF. Basal plus basal-bolus approach in type 2 diabetes. Diabetes Technol Ther 2011;13(Suppl. 1): S75–S83
13. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384–1395
14. Gross JL, Kramer CK, Leitão CB, et al.; Diabetes and Endocrinology Meta-analysis Group (DEMA). Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med 2011;154:672–679
15. Carver C. Insulin treatment and the problem of weight gain in type 2 diabetes. Diabetes Educ 2006;32:910–917
16. Bush MA, Matthews JE, De Boever EH, et al. Safety, tolerability, pharmacodynamics and pharmacokinetics of albiglutide, a long-acting glucagon-like peptide-1 mimetic, in healthy subjects. Diabetes Obes Metab 2009;11:498–505
17. Madsbad S, Kielgast U, Asmar M, Deacon CF, Torekov SS, Holst JJ. An overview of once-weekly glucagon-like peptide-1 receptor agonists–available efficacy and safety data and perspectives for the future. Diabetes Obes Metab 2011;13:394–407
18. Rosenstock J, Stewart MW. Albiglutide. Glucagon-like peptide GLP-1 receptor agonist, treatment of type 2 diabetes. Drugs Future 2010;35:701–712
19. Rosenstock J, Reusch J, Bush M, Yang F, Stewart M; Albiglutide Study Group. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. Diabetes Care 2009;32:1880–1886
20. Tomkin GH. Albiglutide, an albumin-based fusion of glucagon-like peptide 1 for the potential treatment of type 2 diabetes. Curr Opin Mol Ther 2009;11:579–588
21. Seino Y, Nakajima H, Miyahara H, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of albiglutide, a long-acting GLP-1-receptor agonist, in Japanese subjects with type 2 diabetes mellitus. Curr Med Res Opin 2009;25:3049–3057
22. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(Suppl. 1):S1–S266
23. Young MA, Wald JA, Matthews JE, Yang F, Reinhardt RR. Effect of renal impairment on the pharmocokinetics, efficacy, and safety of albiglutide. Postgrad Med 2014;126:35–36
24. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379
25. Ahrén B, Stewart M, Cirkel D, et al. Weekly GLP-1 receptor agonist albiglutide is superior to sitagliptin or glimepiride in patients with type 2 diabetes mellitus on metformin at the 104 week primary endpoint. Diabetes Care 2014;37: 2141–2148
26. Pratley R, Stewart M, Cirkel D, Ye J, Perry C, Carr MC. Harmony 4: 52-week efficacy of albiglutide vs insulin glargine in patients with type 2 diabetes mellitus. Diabetologia 2013;56(Suppl. 1):S360–S361
27. Nauck M, Stewart M, Perkins C, et al. Harmony 2 results at week 52 primary endpoint: once-weekly albiglutide monotherapy for patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetologia 2013;56(Suppl. 1):S360
28. Reusch J, Stewart M, Perkins C, et al. Harmony 1 results at week 52 primary endpoint: once-weekly albiglutide vs placebo in patients with type 2 diabetes mellitus not controlled on pioglitazone ± metformin. Diabetologia 2013; 56(Suppl. 1):S359–S360
29. Stewart M, Yang F, Perry C, Carr MC, Home PD. 52-week efficacy of albiglutide vs placebo vs pioglitazone in triple therapy (background metformin and glimepiride) in patients with type 2 diabetes: Harmony 5 study. Diabetologia 2013; 56(Suppl. 1):S361