

Weekly glucagon-like peptide-1 receptor agonist albiglutide as monotherapy improves glycemic parameters in Japanese patients with type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled study

Antonio Nino¹, Inaha Okuda², Timothy H Wilson³, Lynn Yue¹, Hiromu Nakajima², Maho Tsuboi², Molly C Carr¹, Yutaka Seino^{4*}

¹GlaxoSmithKline, Collegeville, PA, USA, ²GlaxoSmithKline, Tokyo, Japan, ³PAREXEL International, Durham, NC, USA, and ⁴Kansai Electric Power Hospital, Osaka, Japan

Keywords

Glucagon-like peptide 1, Japan, Type 2 diabetes mellitus

*Correspondence

Yutaka Seino

Tel.: +81-6-6422-7354

Fax: +81-6-6458-8758

E-mail address:

seino.yutaka@e2.kepco.co.jp

J Diabetes Investig 2018; 9: 558–566

doi: 10.1111/jdi.12749

Clinical Trial Registry

ClinicalTrials.gov

NCT01733758

ABSTRACT

Aims/Introduction: The present phase 3, randomized, double-blind 24-week study with extension to 1 year assessed the efficacy and safety of albiglutide compared with placebo in Japanese patients with type 2 diabetes mellitus inadequately controlled by diet and exercise with or without a single oral antidiabetic drug.

Materials and Methods: Patients received weekly albiglutide 30 mg ($n = 160$), albiglutide 50 mg ($n = 150$) or a placebo switched to albiglutide 30 mg after 24 weeks ($n = 77$). Open-label daily liraglutide 0.9 mg ($n = 103$) was included as a reference. Oral antidiabetic drug use was discontinued before baseline. The primary end-point was 24-week change from baseline in glycated hemoglobin (HbA1c). Secondary end-points included fasting plasma glucose, bodyweight and adverse events.

Results: At 24 weeks, mean HbA1c changes from baseline were -1.10 , -1.30 , and 0.25% for albiglutide 30, 50 mg and placebo, respectively (P vs placebo <0.0001 for both albiglutide doses), -1.19% for liraglutide. Decreases in HbA1c with albiglutide were sustained through the study. Mean fasting plasma glucose decreased by ≥ 20 mg/dL, and the mean change in bodyweight was ≤ 0.5 kg through 1 year across groups. Most commonly reported adverse events were nasopharyngitis, constipation and nausea. The incidence of adverse events was higher in active treatment groups than in the placebo group. Few hypoglycemia events were reported; no patient withdrew as a result of hypoglycemia. No new safety signals were detected.

Conclusions: Albiglutide monotherapy achieved clinically significant decreases in HbA1c and fasting plasma glucose with good tolerability in Japanese patients with type 2 diabetes mellitus inadequately controlled by diet and exercise with or without a single oral antidiabetic drug.

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) receptor agonists stimulate the incretin system, enhancing the secretion of insulin from pancreatic β -cells in response to ingested glucose¹. GLP-1 receptor agonists have become an important treatment option for

patients with type 2 diabetes mellitus. Albiglutide is a GLP-1 receptor agonist generated by fusion of a dipeptidyl peptidase-4-resistant GLP-1 dimer to human serum albumin. The extended half-life (approximately 5 days) of albiglutide allows for once-weekly subcutaneous administration. In the HARMONY series of phase 3 studies, albiglutide was effective in improving glycemic parameters as monotherapy or in

Received 25 May 2017; revised 21 August 2017; accepted 13 September 2017

combination with oral antidiabetic drugs (OADs) in primarily Caucasian adults with type 2 diabetes mellitus²⁻⁸.

Type 2 diabetes mellitus in East Asian individuals is largely dependent on β -cell dysfunction⁹⁻¹², and meta-analyses show incretin-based drugs to have greater efficacy in Asian than non-Asian dominant studies¹³⁻¹⁵. Experience with albiglutide in Japanese patients with type 2 diabetes mellitus includes two short-term, phase 2 studies^{16,17}. These studies showed that albiglutide improves glycemic parameters and is well tolerated in this patient population.

Here, we present the results of a 1-year, phase 3 study evaluating the efficacy and safety of albiglutide 30 or 50-mg monotherapy compared with a placebo in Japanese patients with type 2 diabetes mellitus whose disease was inadequately controlled by diet and exercise, either alone or in combination with a single OAD.

METHODS

Study design and patient population

The present study was carried out in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice, all applicable patient privacy requirements and the ethical principles outlined in the Declaration of Helsinki (2008). The protocol was approved by investigational center ethics committees or institutional review boards, and written informed consent was obtained from each patient before any study-specific procedure was carried out. The study is registered at ClinicalTrials.gov under the number NCT01733758.

In the present phase 3, 24-week, randomized, double-blind, placebo-controlled study, with an extension to 1 year, patients

were randomized to a matching placebo, one of two albiglutide arms (once weekly) or open-label liraglutide (Figure 1). The dosage of albiglutide was started at 30 mg for both albiglutide groups. One albiglutide group remained at the 30-mg dose throughout the study, whereas albiglutide was increased to 50 mg at week 4 in the other treatment group. The open-label liraglutide arm (started at 0.3 mg once daily, then titrated up to 0.6 and 0.9 mg after 1 and 2 weeks, respectively) was included as an active comparator reference arm only, as required by the Japanese Pharmaceuticals and Medical Devices Agency. Liraglutide 0.9 mg is the maximum dose approved in Japan.

Study assessments were scheduled at week -8 to -4 (screening), week -2 (washout/run-in) and week 0 (baseline); thereafter, visits were scheduled at weeks 4, 8, 11, 12, 16, 21, 24, 28, 40 and 52; a follow-up visit was scheduled for week 60.

Eligible patients had type 2 diabetes mellitus that was inadequately controlled on a regimen of diet and exercise alone or diet and exercise with a single OAD (including a biguanide, glinide, sulfonylurea, α -glucosidase inhibitor or dipeptidyl peptidase-4 inhibitor) for at least 8 weeks before screening. For patients being treated with diet and exercise alone, glycated hemoglobin (HbA1c) had to be ≥ 7.0 and $\leq 10.0\%$ at screening and at visit 2. For patients being treated with diet and exercise and a single OAD, HbA1c had to be ≥ 6.5 and $\leq 9.5\%$ at screening, and ≥ 7.0 and $\leq 10\%$ at visit 2.

Excluded were patients with type 1 diabetes mellitus, clinically significant cardiovascular and/or cerebrovascular disease, current biliary disease, clinical signs or symptoms of or a history of pancreatitis, personal history or family history of medullary thyroid carcinoma, or prior use of a thiazolidinedione or GLP-1 receptor agonist within 4 months before screening.

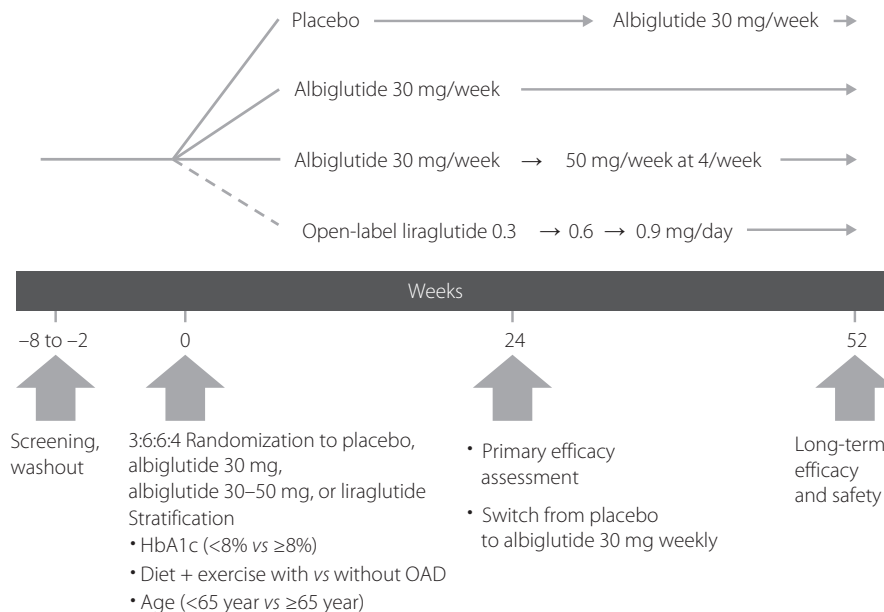


Figure 1 | Study design. HbA1c, glycated hemoglobin; OAD, oral antidiabetic drug.

Patients currently receiving a single OAD were asked to discontinue their OAD during the 4- to 8-week washout/run-in period and throughout the duration of the study.

Study objectives

The primary end-point was change from baseline in HbA1c with albiglutide vs placebo at week 24. Secondary end-points included change from baseline to week 24 in fasting plasma glucose (FPG); changes from baseline over time in HbA1c, FPG and body weight; the proportion of patients achieving target HbA1c treatment goals of <6.5 and <7.0%; time to study withdrawal; and rates of adverse events (AEs), serious AEs (SAEs) and hypoglycemic events.

Assessments

Blood samples for assessments, including HbA1c and FPG, were taken before administration of the investigational product at study visits. Glycemic evaluations were carried out at a central laboratory. The presence of anti-albiglutide antibodies was assessed in all patients, except those in the open-label liraglutide arm, using a validated enzyme-linked immunosorbent assay. Selected anti-GLP-1-positive samples were further tested for GLP-1 neutralizing activity. Immunogenicity sampling was carried out at visit 3 (baseline), and weeks 12, 24, 40, 52 (end-of-treatment visit) and 60 (follow-up visit).

Safety assessments included SAEs and AEs, which included AEs of special interest, such as hypoglycemic events, gastrointestinal events, injection-site reactions, potential systemic allergic reactions, thyroid tumors, cardiovascular events, atrial fibrillation and atrial flutter, pneumonia, diabetic retinopathy, pancreatitis, appendicitis, and liver events. Clinical laboratory evaluations, physical examinations, 12-lead electrocardiograms and vital signs were also assessed.

Criteria for protocol-specified withdrawal for hyperglycemia

Patients were withdrawn from the study if they met the protocol-specified definition for hyperglycemia: FPG ≥ 15.5 mmol/L (≥ 280 mg/dL) between week 2 and week 4; FPG ≥ 13.9 mmol/L (≥ 250 mg/dL) between week 4 and week 12; or FPG ≥ 12.8 mmol/L (≥ 230 mg/dL) between week 12 and week 52.

Statistical analysis

Change from baseline in HbA1c and FPG at weeks 24 and 52 were analyzed using an analysis of covariance model with group (excluding the liraglutide arm), prior diabetes therapy and age category (<65 vs ≥ 65 years) as factors, and baseline HbA1c as a continuous covariate. The primary analyses were carried out on the intention-to-treat population (all patients with a baseline assessment and at least one post-baseline assessment of HbA1c) using a last observation carried forward algorithm. Change from baseline over time in HbA1c, FPG and bodyweight was evaluated descriptively. The proportion of patients achieving HbA1c responses of <6.5 or <7% was analyzed by the Cochran–Mantel–Haenszel test, adjusting for

baseline HbA1c, prior diabetes therapy and age. Albiglutide 30 and 50 mg were compared with a placebo for time to withdrawal for any reason or due to hyperglycemia using pairwise log-rank tests. No statistical analyses were carried out against the liraglutide reference group. The safety population included all randomized patients who received at least one dose of study treatment. Descriptive summaries of AEs and SAEs are presented.

Randomized treatment assignment was based on a sequestered, fixed randomization schedule that was computer generated and implemented through an interactive voice response system established by the sponsor. Both patients and investigators were blinded to the albiglutide and placebo treatment assignments. Eligible patients were stratified by HbA1c level (<8.0 vs ≥ 8.0 %) at visit 2, current diabetes therapy at screening (diet and exercise alone vs diet and exercise with a single OAD therapy) and age (<65 vs ≥ 65 years). The study of approximately 375 patients randomized to three blinded treatment groups in a 2:2:1 ratio had at least a 95% power to reject the null hypothesis of no treatment benefit if the actual albiglutide treatment superiority was no smaller than 0.6% and the standard deviation for HbA1c change from baseline was no larger than 1.1%.

RESULTS

The study was carried out in 75 centers in Japan between 22 February 2013 and 23 February 2015.

Patients

Patient disposition is shown in Figure 2. A total of 494 patients were enrolled. Patients randomized and receiving at least one dose of study treatment (safety population, $n = 490$) included those treated with a placebo ($n = 77$), albiglutide 30 mg ($n = 160$), albiglutide 30 mg titrated up to 50 mg at week 4 ($n = 150$) or liraglutide ($n = 103$). A total of 50 patients discontinued treatment; 21 patients discontinued due to AEs (Figure 2). Treatment groups were well balanced at baseline (Table 1).

Efficacy

Change from baseline in HbA1c and FPG levels

Mean decreases from baseline in HbA1c levels were observed over time in all active treatment groups (Figure 3a). Declines in all active treatment groups were >1% by week 12, and were maintained through week 52. At week 24, changes from baseline in HbA1c (standard error [SE]) before applying the statistical model were 0.24% (0.72%), -1.08% (0.62%), -1.32% (0.70%) and -1.19% (0.64%), respectively, for the placebo, albiglutide 30 mg, albiglutide 50 mg and liraglutide. HbA1c increased slightly in the placebo group (before switching to albiglutide 30 mg) from baseline to week 24, then decreased after albiglutide treatment was started.

As shown in Figure 3b, at week 24, the model-adjusted least squares mean change from baseline in HbA1c [SE] in groups

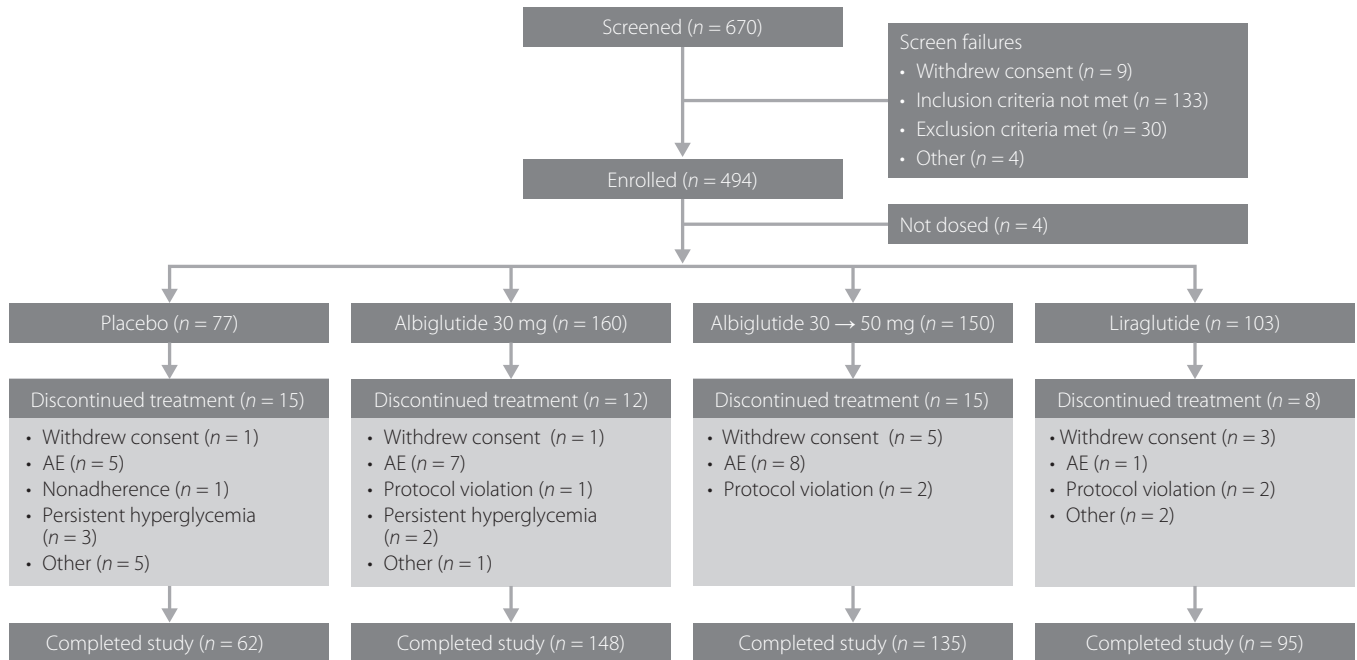


Figure 2 | Patient disposition. AE, adverse event.

Table 1 | Baseline patient demographics and characteristics

	Placebo (n = 77)	Albiglutide 30 mg (n = 160)	Albiglutide 50 mg (n = 150)	Liraglutide (n = 103)
Mean age, years (SD)	57.3 (11.27)	59.6 (9.00)	57.7 (9.51)	58.4 (9.72)
Male, n (%)	52 (67.5)	125 (78.1)	114 (76.0)	81 (78.6)
Mean bodyweight, kg (SD)	68.7 (12.09)	69.3 (13.53)	71.5 (12.91)	72.7 (13.76)
Mean body mass index, kg/m ² (SD)	25.6 (3.42)	25.3 (4.17)	26.1 (3.66)	26.3 (4.35)
Mean duration of diabetes, years (SD)	6.7 (5.38)	7.2 (6.22)	6.9 (6.21)	5.8 (4.37)
Mean baseline HbA1c, % (SD)	8.16 (0.88)	8.07 (0.78)	8.15 (0.83)	8.07 (0.79)
Mean baseline FPG, mg/dL (SD)	159.3 (37.07)	157.3 (33.74)	158.7 (32.82)	157.2 (31.22)
Prior diabetes therapy, n (%)				
Diet + exercise	49 (63.6)	99 (61.9)	95 (63.3)	65 (63.1)
Diet + exercise + 1 OAD	28 (36.4)	61 (38.1)	55 (36.7)	38 (36.9)

FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; OAD, oral antidiabetic drug; SD, standard deviation.

receiving albiglutide 30 mg (−1.10% [0.05]) and albiglutide 50 mg (−1.30% [0.05]) were significantly greater than the placebo (0.25% [0.07], $P < 0.0001$). At week 52, the change from baseline with albiglutide 50 mg (−1.30% [0.06]) was significantly greater than in patients initiated on the placebo who had been switched at 24 weeks to albiglutide 30 mg (−1.08 [0.08], $P = 0.028$). At 52 weeks, the change in HbA1c in patients treated with albiglutide 30 mg (−1.10 [0.05]) was similar to that of the placebo group after switching to albiglutide 30 mg.

The percentages of patients achieving HbA1c target goals of <6.5 and <7.0% at weeks 24 and 52 are shown in Figure 4. The percentage of patients achieving the HbA1c target goals of both <6.5 and <7.0% at 24 weeks was significantly higher in both albiglutide groups compared with the placebo

($P \leq 0.0001$), and the percentage of patients achieving the HbA1c level of <6.5% at week 52 was significantly higher in the albiglutide 50-mg group compared with patients switched from the placebo to albiglutide 30 mg ($P = 0.014$).

Figure 5a shows the change in FPG over time. FPG declines in all active treatments were >25 mg/dL by week 4, and remained low through week 52. Model-adjusted least squares mean change from baseline showed a pattern similar to that of HbA1c (Figure 5b). At week 24, decreases from baseline in FPG (SE) for both albiglutide 30 mg (−25.4 [1.8] mg/dL) and albiglutide 50 mg (−29.5 [1.8] mg/dL) were significantly different from the placebo (7.9 [2.5] mg/dL, $P < 0.0001$). At week 52, changes in FPG (SE) in patients receiving albiglutide 50 mg (−31.3 [1.7] mg/dL) were significantly greater than for the

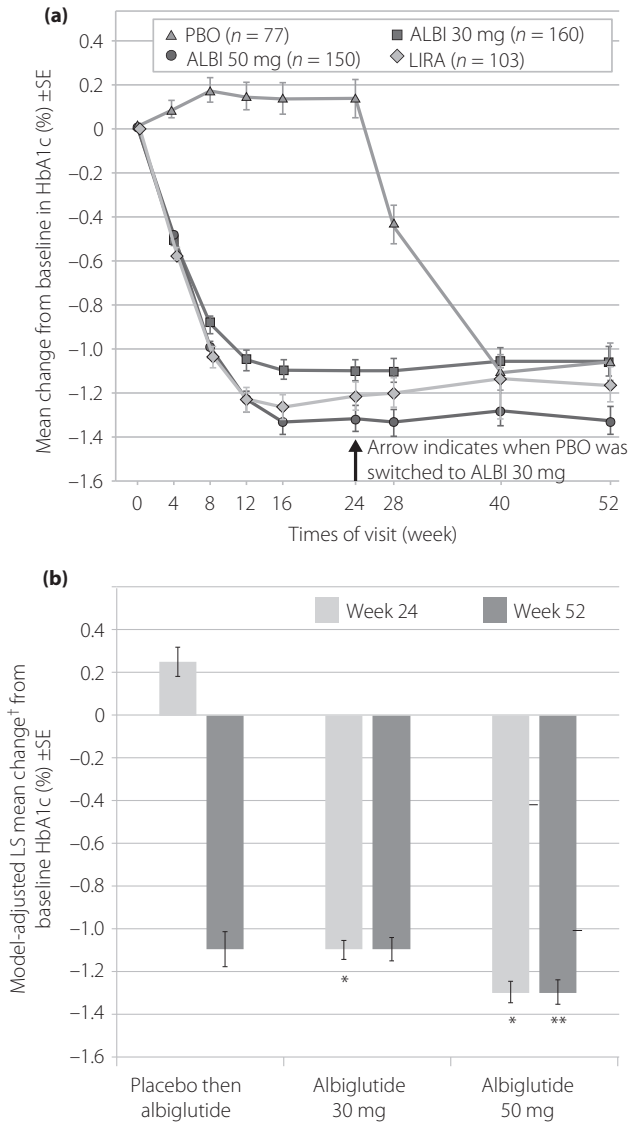


Figure 3 | Change from baseline in glycated hemoglobin (HbA1c; %) (a) over time (mean \pm standard error [SE]), and (b) at weeks 24 and 52 (mean \pm SE). No statistical analyses were carried out against the open-label liraglutide reference group. [†]Adjusted for treatment group (excluding liraglutide), baseline HbA1c, prior diabetes treatment (with or without an oral antidiabetic drug) and age. ALBI, albiglutide; LIRA, liraglutide; LS, least squares; PBO, placebo. * $P < 0.0001$ vs placebo. ** $P = 0.0282$ vs placebo.

placebo switched to albiglutide 30-mg group (-24.3 [2.6] mg/dL, $P = 0.025$), and the changes in patients continually receiving albiglutide 30 mg (-24.1 [1.7]) were similar to those of the placebo group after switching to albiglutide 30 mg.

Bodyweight

Mean changes in bodyweight were minimal and within ± 0.5 kg of baseline in all treatment groups at week 24 (ranging from 0.32 kg in the albiglutide 30-mg group to -0.50 kg in the

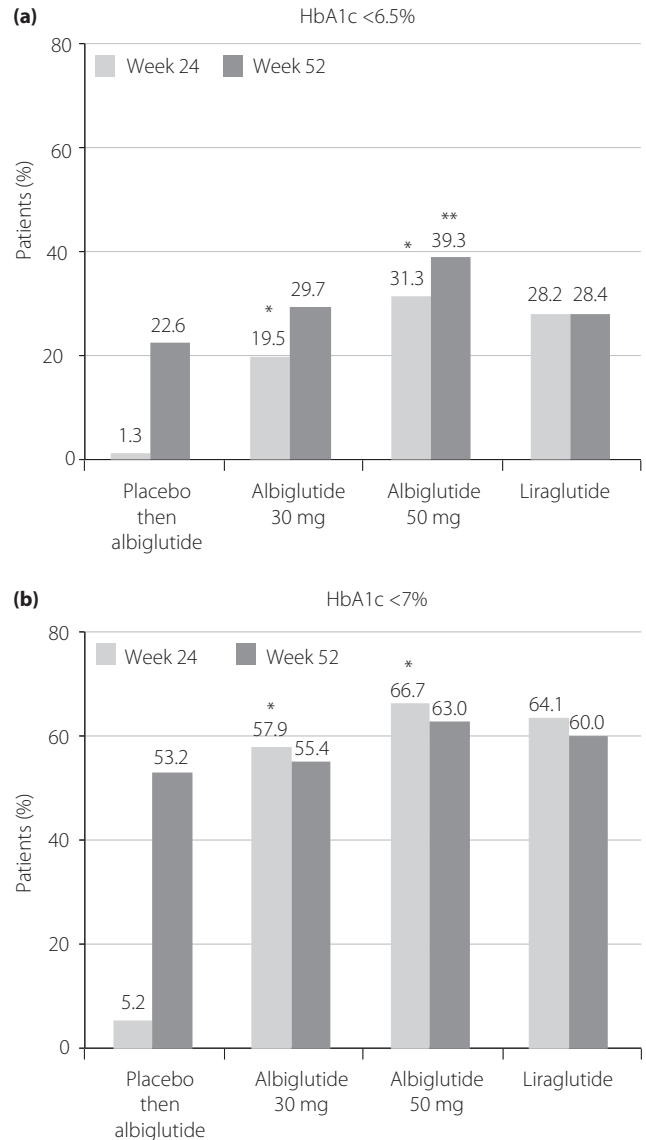


Figure 4 | Percentage of patients achieving target glycated hemoglobin (HbA1c) of (a) $<6.5\%$ and (b) $<7\%$ at weeks 24 and 52 in the randomized groups. Adjusted for baseline HbA1c, prior diabetes treatment (with or without an oral antidiabetic drug), and age. * $P \leq 0.0001$ vs placebo. ** $P = 0.014$ vs placebo.

placebo group) and at week 52 (ranging from 0.08 kg in the albiglutide 30-mg group to -0.50 kg in the liraglutide group).

Time to study withdrawal

By week 24, 12 (15.6%), seven (4.4%), and nine (6.0%) patients had withdrawn from the study in the placebo, albiglutide 30-mg and albiglutide 50-mg groups, respectively. By week 52, 15 (19.5%), 12 (7.5%), and 15 patients (10.0%) had withdrawn from the study in the placebo, albiglutide 30 and albiglutide 50-mg groups, respectively (see Figure 2 for reasons for withdrawal). Log-rank comparison showed that over the course of

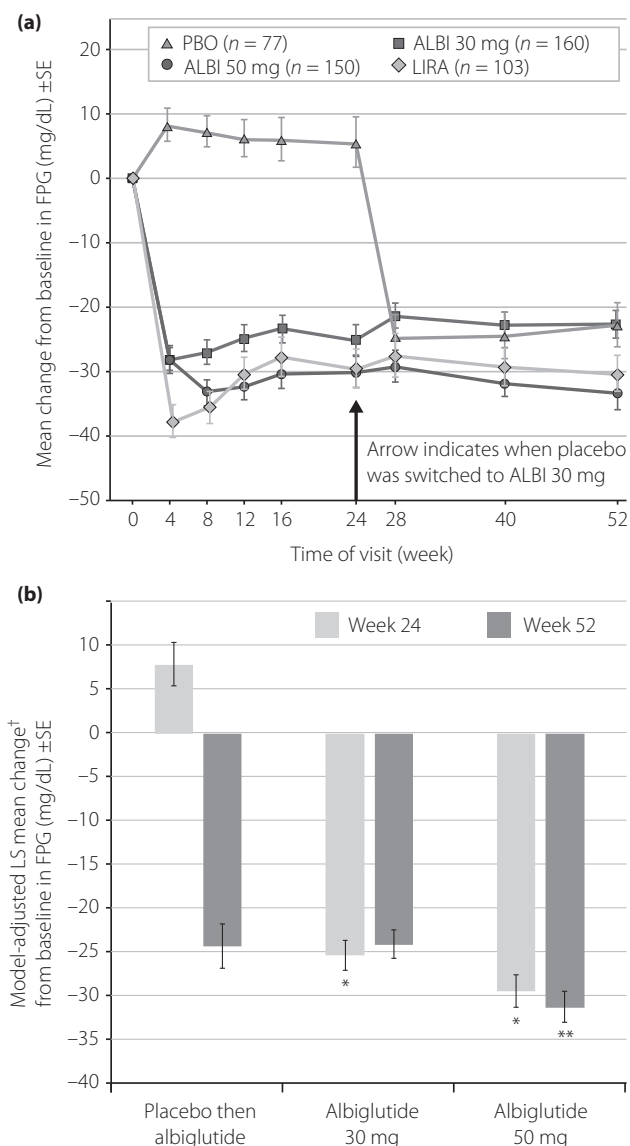


Figure 5 | Change from baseline in fasting plasma glucose (FPG; mg/dL) (a) over time (mean \pm standard error [SE]) in all treatment groups, and (b) at weeks 24 and 52 (mean \pm SE) in the randomized groups. No statistical analyses were carried out against the open-label liraglutide reference group. †Adjusted for treatment group (excluding liraglutide), baseline HbA1c, prior diabetes treatment (with or without an oral antidiabetic drug) and age. * $P < 0.0001$ vs placebo. ** $P = 0.0247$ vs placebo. ALBI, albiglutide; LIRA, liraglutide; LS, least squares; PBO, placebo.

the study, the time to withdrawal was significantly longer for the albiglutide 30-mg group ($P = 0.0059$) and the albiglutide 50-mg group ($P = 0.0322$) compared with the placebo group.

Withdrawals for hyperglycemia

One patient in the placebo group (at week 6) and one patient in the albiglutide 30-mg group (at week 29) were withdrawn

from the study due to protocol-specified hyperglycemia criteria. Two additional patients in the placebo group and one patient in the albiglutide 30-mg group were withdrawn from the study at the investigator's discretion due to persistent hyperglycemia. These three patients did not meet the protocol-specified criteria for withdrawal for hyperglycemia.

Safety

AEs

After 52 weeks, the frequencies of any AE ranged from 58.5% of patients in the placebo group, after the switch to albiglutide 30 mg, to 83.3% of patients in the albiglutide 50-mg group (Table 2). Most AEs were rated as 'mild' or 'moderate' in intensity across all groups; just four (2.5%) and two (1.3%) patients in the albiglutide 30 and 50-mg groups, respectively, reported an AE that was rated as 'severe.'

Table 3 shows the most commonly reported AEs through week 52. The frequency of any on-therapy hypoglycemic event was 2.6% ($n = 2$) for placebo before switching and 4.6% ($n = 3$) after switching to albiglutide, 5.0% ($n = 8$) for albiglutide 30 mg, 4.0% ($n = 6$) for albiglutide 50 mg, and 2.9% ($n = 3$) for liraglutide. None of these AEs was serious or led to withdrawal of active treatment.

Gastrointestinal events

Nausea was among the most common AEs (Table 3). There were no severe events of nausea during the study, and no patients were withdrawn due to an AE of nausea. A total of 16 patients experienced AEs of nausea, considered treatment-related (three patients in the placebo group before switching to albiglutide and two after switching, two patients receiving albiglutide 30 mg, and nine patients receiving albiglutide 50 mg).

A total of eight events of on-therapy vomiting were reported (in $<2\%$ of patients). All AEs of vomiting were mild, and none led to withdrawal of study medication. Four patients experienced treatment-related vomiting (one in the placebo group before switching to albiglutide, one in the albiglutide 30-mg group and two in the albiglutide 50-mg group).

The frequency of diarrhea is shown in Table 3. There were no events of diarrhea rated as severe during the study, and no patients were withdrawn due to an AE of diarrhea. Seven patients experienced events of diarrhea that were considered treatment-related (two patients in the placebo group before switching, three in the albiglutide 50-mg group and two in the liraglutide group).

Serious AEs

A total of 11 patients (all in the albiglutide 30 and 50-mg groups) experienced a total of 13 SAEs through week 52. Six SAEs of neoplasm were reported including breast cancer ($n = 1$, albiglutide 50 mg), gastric cancer ($n = 1$, albiglutide 50 mg), lymphoma ($n = 1$, albiglutide 50 mg), pancreatic cancer ($n = 1$, albiglutide 30 mg), plasma cell myeloma ($n = 1$,

Table 2 | Summary of adverse events occurring through week 52

	Placebo before switch to albiglutide 30 mg (n = 77)		Placebo after switch to albiglutide 30 mg (n = 65)		Albiglutide 30 mg (n = 160)		Albiglutide 50 mg (n = 150)		Liraglutide (n = 103)	
	n (%)	No. events	n (%)	No. events	n (%)	No. events	n (%)	No. events	n (%)	No. events
Any AE	47 (61.0)	110	38 (58.5)	94	129 (80.6)	467	125 (83.3)	517	78 (75.7)	246
Any on-therapy AE	44 (57.1)	96	37 (56.9)	91	126 (78.8)	427	124 (82.7)	489	74 (71.8)	225
Any treatment-related AE	9 (11.7)	14	9 (13.8)	18	31 (19.4)	120	40 (26.7)	168	17 (16.5)	29
Any SAE	0	0	0	0	5 (3.1)	6	6 (4.0)	7	0	0
Any AE leading to withdrawal of active treatment and/or withdrawal from study	3 (3.9)	3	2 (3.1)	2	7 (4.4)	7	8 (5.3)	8	1 (1.0)	1
On-therapy AE rate [†]		282.1		213.4		246.0		301.5		199.5
Total person-years [‡]		340		42.6		173.6		162.2		112.8

[†]On-therapy adverse event (AE) rate is the number of on-therapy AEs per 100 person-years. [‡]Total person-years is defined as the cumulative study treatment exposure duration for all patients in the treatment group during the on-therapy treatment period. SAE, serious adverse event.

Table 3 | Most common (≥5% of patients) adverse events occurring through week 52

	Placebo before switch to albiglutide 30 mg (n = 77)		Placebo after switch to albiglutide 30 mg (n = 65)		Albiglutide 30 mg (n = 160)		Albiglutide 50 mg (n = 150)		Liraglutide (n = 103)	
	n (%)	No. AEs/rate [†]	n (%)	No. AEs/rate [†]	n (%)	No. AEs/rate [†]	n (%)	No. AEs/rate [†]	n (%)	No. AEs/rate [†]
Nasopharyngitis	18 (23.4)	21/61.71	10 (15.4)	12/28.15	45 (28.1)	60/34.56	34 (22.7)	48/29.59	25 (24.3)	33/29.26
Diarhea	4 (5.2)	6/17.63	0	0	2 (1.3)	2/1.15	8 (5.3)	8/4.93	5 (4.9)	5/4.43
Eczema	4 (5.2)	4/11.75	2 (3.1)	2/4.69	2 (1.3)	2/1.15	4 (2.7)	5/3.08	2 (1.9)	2/1.77
Nausea	4 (5.2)	4/11.75	3 (4.6)	3/7.04	2 (1.3)	2/1.15	10 (6.7)	15/9.25	4 (3.9)	4/3.55
Constipation	3 (3.9)	3/8.82	3 (4.6)	3/7.04	14 (8.8)	14/8.06	17 (11.3)	19/11.71	7 (6.8)	7/6.21
Upper respiratory tract inflammation	3 (3.9)	4/11.75	0	0	8 (5.0)	8/4.61	2 (1.3)	2/1.23	3 (2.9)	4/3.55
Bronchitis	2 (2.6)	2/5.88	2 (3.1)	2/4.69	4 (2.5)	5/2.88	8 (5.3)	8/4.93	2 (1.9)	2/1.77
Back pain	1 (1.3)	1/2.94	2 (3.1)	2/4.69	8 (5.0)	10/5.76	4 (2.7)	4/2.47	3 (2.9)	3/2.66
Pharyngitis	1 (1.3)	1/2.94	0	0	13 (8.1)	17/9.79	1 (0.7)	1/0.62	2 (1.9)	2/1.77
Injection-site erythema	0	0	1 (1.5)	2/4.69	3 (1.9)	5/2.88	9 (6.0)	69/42.54	0	0

[†]Adverse event (AE)/rate is the number of on-therapy AEs per 100 person-years.

albiglutide 50 mg) and rectal cancer ($n = 1$, albiglutide 30 mg). One SAE (pancreatic cancer in the albiglutide 30-mg group) was considered treatment-related.

Other SAEs, occurring in one patient each, included Rathke's cleft cyst (albiglutide 50 mg), macular edema (albiglutide 30 mg), cholecystitis (albiglutide 30 mg), pulmonary tuberculosis (albiglutide 30 mg), spinal compression fracture (albiglutide 50 mg), cerebellar hemorrhage (albiglutide 30 mg) and acute renal failure (albiglutide 50 mg).

Three on-therapy deaths occurred during the study ($n = 2$, albiglutide 30 mg; $n = 1$, albiglutide 50 mg). One death was considered related to study medication; a 65-year-old patient in the albiglutide 30-mg group experienced a fatal, on-therapy SAE (pancreatic cancer) 196 days after the first dose and 7 days after the last dose of albiglutide.

Antidrug antibodies

Treatment-induced antidrug antibodies were reported in 34 of 387 (8.8%) patients treated with albiglutide. No neutralizing antibodies were detected. Mean change from baseline (standard deviation) in HbA1c was comparable between antibody-positive and antibody-negative patients: -1.02% (0.99%) and -1.19% (0.75%), respectively.

DISCUSSION

The results of the present long-term study of albiglutide in Japanese patients with type 2 diabetes mellitus show that weekly albiglutide monotherapy exhibited favorable characteristics in safety and efficacy in Japanese patients with type 2 diabetes mellitus inadequately controlled by diet and exercise with or without a single OAD. This study is the first to show that long-term albiglutide monotherapy in Japanese patients with type 2 diabetes mellitus is well tolerated and improves glycemic measures. These results extend previous findings of safety and efficacy in short-term studies of Japanese patients^{16,17}. The effectiveness of albiglutide in Japanese patients is of particular interest, because the drug targets pancreatic β -cell dysfunction, which is the primary deficit in type 2 diabetes mellitus of East Asian patients^{9–12}. In meta-analyses, incretin-based drugs are seen to have greater efficacy in Asian compared with non-Asian populations, without major differences in safety^{13–15}.

The current study met its primary end-point, with albiglutide monotherapy leading to clinically and statistically significant reductions in HbA1c levels. Albiglutide monotherapy was effective in lowering both HbA1c and FPG, with improvements maintained throughout the 52-week study. More patients in the albiglutide groups achieved the target treatment goals of <6.5 and $<7.0\%$ HbA1c compared with the placebo at week 24. By week 52, after patients in the placebo group had been switched to albiglutide 30 mg, the percentage of patients achieving the target treatment goal of $<7.0\%$ HbA1c was similar across all albiglutide groups. Although liraglutide was included only as a reference arm, changes in glycemic parameters in this group were generally comparable with those observed in the

albiglutide groups. Changes in bodyweight were minimal (within ± 0.5 kg of baseline) in all groups over the course of the study. The rate of treatment-induced antidrug antibodies against albiglutide was low (8.8%) and was not treatment limiting, as no neutralizing antibodies were detected. HbA1c lowering was comparable between patients who were positive or negative for anti-albiglutide antibodies. However, because of the small number of antibody-positive patients, no conclusions about the impact of the antibodies on efficacy or safety can be drawn.

Albiglutide was generally well tolerated at both dosages, with comparable rates of AEs across active treatment groups. The most commonly reported AEs were nasopharyngitis, constipation and nausea. The rates of gastrointestinal events, a class of AE consistent with the known profile of GLP-1 agonists, were low and consistent across treatment groups. The rates of diarrhea and nausea were highest in the albiglutide 50-mg group (5.3 and 6.7%, respectively), but it should be noted that diarrhea and nausea rates in the placebo group before switching to albiglutide were only slightly lower (5.2% for both). SAEs were observed in 11 patients, all of whom were receiving albiglutide. One SAE (pancreatic cancer) was considered to be related to study medication. This SAE also accounted for the only death related to study medication.

A limitation of the present study was that the active comparator, liraglutide, was open-label and not included in the statistical analyses. In addition, the dosage of liraglutide (0.9 mg daily) was only half the maximum dosage permitted in several countries, although it is the maximum liraglutide dosage approved in Japan; therefore, it provides information that is clinically relevant to this patient population. Both doses of albiglutide were comparable with liraglutide for efficacy and safety, although only liraglutide was open-label, and that could have led to bias in safety and efficacy reporting in the liraglutide group. The inclusion of a placebo arm provided the best means with which to test the effectiveness and tolerability of albiglutide monotherapy in this patient population; however, the shorter duration of exposure to placebo and albiglutide (approximately 24 weeks each) in the placebo group should be taken into consideration when comparing a placebo with active treatment.

The results of the present study of Japanese patients with type 2 diabetes mellitus are generally consistent with the large body of evidence obtained in the HARMONY series of albiglutide studies, carried out in a broader population of patients with type 2 diabetes mellitus^{2–8}. The present study showed that albiglutide monotherapy for 52 weeks had a favorable benefit–risk profile in Japanese patients with type 2 diabetes mellitus whose disease was not adequately controlled on diet and exercise with or without a single OAD. It is the first long-term, phase 3 study of albiglutide monotherapy in this patient population. Albiglutide lowered HbA1c significantly compared with the placebo at 24 weeks, provided sustained glycemic control, did not result in weight gain and was generally well tolerated, with no new or unexpected safety concerns.

ACKNOWLEDGMENTS

Editorial support was provided by Pasquale Iannuzzelli, PhD, and Elizabeth Rosenberg, PhD, of AOI Communications, L.P., with funding provided by GlaxoSmithKline. The authors thank the patients and physicians who participated in the study. This study (ClinicalTrials.gov NCT01733758; <https://clinicaltrials.gov/ct2/results?term=NCT01733758&Search=Search>) was funded by GlaxoSmithKline.

DISCLOSURE

AN, IO, LY, HN, MT and MCC are employees of and hold stock in GlaxoSmithKline (GSK); THW is an employee of PAREXEL and holds stock in GSK. YS reports consulting and/or speaker fees from Kao, Kyowa Hakko Kirin, Taisho Pharmaceuticals, Becton Dickinson and Company, Novo Nordisk Pharma, and MSD. YS received speakers' bureau fees from Novo Nordisk, MSD, Takeda Pharmaceuticals, Sanofi, Taisho Toyama Pharmaceuticals, Eli Lilly and Company, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Kowa, Astellas Pharma, and Boehringer Ingelheim.

REFERENCES

1. Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. *Lancet Diabetes Endocrinol* 2016; 4: 525–536.
2. Reusch J, Stewart MW, Perkins CM, *et al.* Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. *Diabetes Obes Metab* 2014; 16: 1257–1264.
3. Nauck MA, Stewart MW, Perkins C, *et al.* Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (HARMONY 2): 52 week primary endpoint results from a randomised, placebo-controlled trial in patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetologia* 2016; 59: 266–274.
4. Ahren B, Johnson SL, Stewart M, *et al.* HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care* 2014; 37: 2141–2148.
5. Weissman PN, Carr MC, Ye J, *et al.* HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. *Diabetologia* 2014; 57: 2475–2484.
6. Home PD, Shamanna P, Stewart M, *et al.* Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. *Diabetes Obes Metab* 2015; 17: 179–187.
7. Rosenstock J, Fonseca VA, Gross JL, *et al.* Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care* 2014; 37: 2317–2325.
8. Pratley RE, Nauck MA, Barnett AH, *et al.* Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol* 2014; 2: 289–297.
9. Fukushima M, Usami M, Ikeda M, *et al.* Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. *Metabolism* 2004; 53: 831–835.
10. Iwahashi H, Okauchi Y, Ryo M, *et al.* Insulin-secretion capacity in normal glucose tolerance, impaired glucose tolerance, and diabetes in obese and non-obese Japanese patients. *J Diabetes Investig* 2012; 3: 271–275.
11. Yabe D, Seino Y, Fukushima M, *et al.* Beta cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. *Curr Diab Rep* 2015; 15: 602.
12. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: focus on East Asian perspectives. *J Diabetes Investig* 2016; 7(suppl 1): 102–109.
13. Park H, Park C, Kim Y, *et al.* Efficacy and safety of dipeptidyl peptidase-4 inhibitors in type 2 diabetes: meta-analysis. *Ann Pharmacother* 2012; 46: 1453–1469.
14. Kim YG, Hahn S, Oh TJ, *et al.* Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. *Diabetologia* 2013; 56: 696–708.
15. Kim YG, Hahn S, Oh TJ, *et al.* Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. *Diabetes Obes Metab* 2014; 16: 900–909.
16. 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.
17. Seino Y, Inagaki N, Miyahara H, *et al.* A randomized dose-finding study demonstrating the efficacy and tolerability of albiglutide in Japanese patients with type 2 diabetes mellitus. *Curr Med Res Opin* 2014; 30: 1095–1106.