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Efficacy and safety of an albiglutide liquid formulation compared with the lyophilized formulation: A 26-week randomized, double-blind, repeat-dose study in patients with type 2 diabetes mellitus

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ABSTRACT

Aims: Compare the efficacy and safety of albiglutide from a ready-to-use, single-dose, auto-injector system with the lyophilized product in patients with type 2 diabetes mellitus (T2DM).

Methods: In this phase 3 study, 308 patients between 18 and 80 years with T2DM and experiencing inadequate glycemic control on their current regimen of diet/exercise alone or in combination with metformin were randomized 1:1 to weekly injections for 26 weeks with an active albiglutide auto-injector and placebo lyophilized dual-chamber cartridge (DCC) pen injector (n = 154) or active albiglutide lyophilized DCC pen injector and placebo liquid auto-injector (n = 154). Participants received liquid or lyophilized albiglutide 30 mg for 4 weeks, and then 50 mg for the remaining 22 weeks. Change in HbA_{1c} and fasting plasma glucose (FPG), pharmacokinetics, and safety were assessed.

Results: In the albiglutide liquid and lyophilized drug product groups, 55.6% (85/153) and 45.5% of patients (70/154) had a baseline $HbA_{1c} \geq 8.0\%$, respectively. The model-adjusted least squares (LS) mean change in HbA_{1c} from baseline at week 26 was −1.1% (95% CI: −1.3, −1.0) and −1.2% (95% CI: −1.3, −1.0; noninferiority $P = 0.0002$) in the albiglutide liquid and lyophilized product groups, respectively. Similarly, the model-adjusted LS mean change in FPG from baseline at week 26 in the albiglutide liquid and lyophilized product groups was −2.2 (95% CI: −2.6, −1.8) mmol/L and −1.9 (95% CI: −2.3, −1.5) mmol/L, respectively. No new safety concerns were identified.

Conclusion: Change from baseline in HbA_{1c} for albiglutide liquid was noninferior to lyophilized drug product in patients with T2DM.

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1. Introduction

Albiglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist generated through a genetic fusion of 2 modified recombinant human GLP-1 molecules linked in tandem to recombinant human albumin [1–3]. Albiglutide provides sustained blood glucose control in patients with type 2 diabetes mellitus (T2DM) [3]. Albiglutide's long half-life (approximately 5 days) permits once-weekly dosing [3–5].

Albiglutide has been marketed in a dual-chamber cartridge (DCC) single-dose pen-injector containing a lyophilized drug that had to be reconstituted with diluent prior to use. To simplify drug administration, a liquid formulation of albiglutide was developed that could be administered via a ready-to-use, single-dose, auto-injector system that does not require reconstitution.

The pharmacokinetics of single doses of the liquid and lyophilized albiglutide products were previously compared in healthy volunteers [6]. The results showed that the 50-mg albiglutide liquid and lyophilized formulations from the auto-injector and DCC pen-injector, respectively, are bioequivalent. No new safety signals were noted in the bioequivalence study, and the rate and type of adverse events (AEs) reported with the albiglutide 50-mg liquid drug formulation were consistent with the known profile of the lyophilized product [5–7].

Following the bioequivalence study in healthy volunteers, the efficacy and safety of the liquid and lyophilized products were compared in this phase 3 trial in patients with T2DM who failed to achieve optimal glycemic control with diet and exercise alone or in combination with metformin.

2. Patients and methods

2.1. Participants

Adults aged ≥18 to ≤80 years with T2DM and experiencing inadequate glycemic control on their current regimen of diet and exercise alone or in combination with a stable dose of metformin were eligible. A stable dose of metformin was defined as at least 1500 mg, or documented maximum tolerated dose as monotherapy if less than 1500 mg, metformin maintained for approximately 8 weeks prior to screening. Eligible participants had a body mass index (BMI) ≤40 kg/m^2, HbA_{1c} between ≥7.0% (≥53 mmol/mol) and ≤ 10.0% (≤86 mmol/mol), normal hemoglobin (≥11 g/dL [≥110 g/L] for men and ≥10 g/dL [≥100 g/L] for women), and normal organ function. Patients diagnosed with type 1 diabetes or who had a personal or family history of multiple endocrine neoplasia type 2; prior or current history of any cancer; pancreatitis; hypoglycemia unawareness; or diabetic complications were excluded from the study.

2.2. Study design

This was a multicenter, phase 3, randomized, repeat-dose study conducted from March 16, 2016 to May 15, 2017 at 153 sites in the United States (clinicaltrials.gov identifier, NCT02683746). A total of 308 patients were randomized.

The primary endpoint of the randomized trial was change from baseline to week 26 in HbA_{1c}. Twenty-six weeks was selected as the time to assess the primary endpoint based on a review of data from the previous phase 2 and 3 studies of the lyophilized albiglutide product. The secondary endpoints were change from baseline to week 26 in fasting plasma glucose (FPG), change in HbA_{1c} and FPG over time, safety including immunogenicity and injection-site reactions (ISRs), and trough pharmacokinetic concentrations of albiglutide after repeat dosing.

The randomized trial comprised 3 study periods: screening (2 weeks), treatment (26 weeks), and, for those patients not entering the extension study, a follow-up visit (8 weeks after end of treatment) (Supplemental Fig. S1).

Alternatively, participants who completed 26 weeks of treatment in the randomized study could enroll in a 26-week extension study (clinicaltrials.gov identifier, NCT02750930) to receive additional treatment with the albiglutide 50-mg liquid drug product. The open-label extension study was terminated on November 2, 2016, by the study sponsor (GlaxoSmithKline) due to the decision to stop marketing albiglutide. The decision was based on commercial considerations and not due to safety or efficacy concerns. At the time of study termination, only 8 patients had completed the randomized study and were enrolled in the open-label extension study. These 8 patients received between 1 and 4 doses of liquid drug product prior to termination of the extension study. The primary endpoint of the open-label extension study was safety.

2.3. Ethics

This study was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, applicable country specific requirements including US 21 Code of Federal Regulations 312.3, and the ethical principles outlined in the Declaration of Helsinki 2013. The protocol was reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board. All participants provided written informed consent prior to study entry.

2.4. Randomization and blinding

Participants were stratified by age (<65 or ≥ 65 years), weight (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin) before randomization in a 1:1 ratio to one of the two treatment arms. Randomization was undertaken via the sponsor's Interactive Voice Response System by study site personnel after the patient entered the trial, and was implemented based on a sequestered fixed randomization schedule. Patients received two injections; one containing an albiglutide product and one containing placebo. Matching placebos for the autoinjector and lyophilized DCC pen injector were used to maintain

blinding. Both patients and investigators or treating physicians were blinded to albiglutide liquid auto-injector and albiglutide lyophilized DCC pen injector. No patient was unblinded during this study.

2.5. Study treatments

The DCC pen-injector contains lyophilized albiglutide formulated with excipients in one chamber and sterile water for injection in the other chamber [6]. This device is designed for manual reconstitution of lyophilized albiglutide prior to use by rotating the pen housing parts. The liquid formulation is administered via a fixed-dose, fully disposable auto-injector system intended for single use and does not contain a preservative.

Participants received 0.5 mL of liquid or lyophilized albiglutide 30 mg once a week subcutaneously in the abdomen, thigh, or upper arm for 4 weeks, and were then up-titrated to a 50-mg dose for the remaining 22 weeks of the study. Down-titration from 50 mg to 30 mg was not permitted. Diet, exercise, and the patient's stable dose of background metformin were unaltered before or during the treatment. For rescue, up-titration of metformin was permitted for subjects who required hyperglycemic rescue and metformin was selected as the rescue medication. Use of other antidiabetic medications were prohibited unless subjects required antidiabetic medication for hyperglycemic rescue. The preferred post-rescue add-on treatment was insulin. Other medications (with the exception of GLP-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, which were prohibited) could be added at the investigator's discretion.

All other concomitant medications were permitted during the study unless it was expressed specifically that the drug's efficacy was contradicted in the albiglutide prescribing information or the patient concerned.

2.6. Study assessments

Blood samples for HbA_{1c} measurements were collected at week −2 (screening), baseline, and weeks 1, 4, 8, 12, 16, 20, and 26 before administration of study treatment and at the follow-up visit 8 weeks after end of treatment. Blood samples for FPG measurements were taken at baseline then weekly from baseline to week 13, and at weeks 16, 20, and 26 prior to administration of study treatment, as well as at the follow-up visit 8 weeks after end of treatment. Blood samples for pharmacokinetic measurements were taken at weeks 12 and 26 before administration of study treatment.

Safety assessments included monitoring for AEs, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, physical examination, and electrocardiograms. With regards to AEs, the duration, severity, causality, and actions taken to resolve them were reported.

All albiglutide lyophilized product pen-injector and liquid product auto-injector failures and user errors were detected, documented, and reported by the investigator throughout the study.

2.7. Immunogenicity assay

Eligible patients had immunogenicity samples taken and analyzed as described previously [6]. Samples positive for both GLP-1 antibodies and drug binding and neutralizing antibodies were tested for GLP-1 neutralizing activity. If baseline antibody levels or a reduction in titer were not achieved by the follow-up visit in patients who had discontinued the study treatment or who did not participate in the 26-week extension study, additional samples for immunogenicity testing were obtained every 30 days following the follow-up visit until baseline antibody levels, or reduced titers, were achieved. Patients eligible for the extension study had immunogenicity samples taken for analysis prior to each dose of drug on weeks 26, 30, 36, at the end of treatment, and at the follow-up visit 8 weeks after the end of treatment.

2.8. Pharmacokinetics assay

Plasma samples were analyzed for albiglutide using a validated analytical method based on enzyme-linked immunosorbent assay (chemiluminescent assay) as described previously [1,6]. The lower limit of quantification was 50 ng/mL from a 20-μL aliquot of EDTA-treated plasma, and the higher limit of quantification was 1500 ng/mL. Pharmacokinetic trough plasma concentration data were summarized by treatment. No formal statistical analyses were conducted.

2.9. Statistical analyses

A sample size of 150 participants in each treatment group was calculated based on an estimate of approximately 133 participants in each group (assuming withdrawal or loss to follow-up for 13% of participants) to provide 90% power to demonstrate noninferiority for HbA_{1c} change from baseline, assuming a non-inferiority margin of 0.4%, an expected treatment group difference of 0.0%, and a common standard deviation of 1%, using a 2-sample, 1-sided t test with significance level of 0.025. The noninferiority margin of 0.40 was selected based on the expected effect of albiglutide lyophilized drug product as active control.

The analysis of the primary efficacy endpoint was conducted using a mixed-effect model with repeated measures (MMRM) in the intent to treat (ITT) population, which included all randomized patients who received at least 1 dose of study treatment and had a baseline assessment. Imputation under the noninferiority null hypothesis for missing data were incorporated [8]. Multiple imputations assuming missing at random were used to replace missing data for change from baseline in HbA_{1c} at week 26 for all patients in both treatment arms, and then to make all the imputed values for the liquid drug product arm worse by the noninferiority margin 0.4.

For patients with missing data, the imputation used mean and variance-covariance from patients in that treatment group. This approach was used for all data missing post withdrawal for patients who were lost to follow-up or withdrew consent.

The MMRM model via PROC MIXED (SAS Institute, North Carolina, US) included HbA_{1c} change from baseline at post-baseline scheduled visits from week 4 up to week 26 as dependent variables; treatment, region, age category, weight category, background antidiabetic therapy, visit week, treatment-by-week interaction, and baseline HbA_{1c}-by-week interaction as fixed effects; baseline HbA_{1c} as a continuous covariate; and patient as a random effect. An unstructured covariance matrix was used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix was decided upon model convergence status and the Akaike information criterion. Treatment effects estimates (and associated CI) of albiglutide liquid drug product were evaluated within this MMRM model as least squares (LS) mean contrasts relative to the lyophilized drug product.

The null hypothesis was tested based on a 1-sided 97.5% CI (with upper bound equal to that of a 2-sided 95% CI) of the treatment difference at week 26, estimated from the multiple imputation/MMRM (ie, combined MMRM results from multiple imputation). The noninferiority margin was set at 0.4%, the expected treatment group difference was 0.0%, and a common standard deviation of 1%, using a 2-sample, 1-sided *t* test with significance level of 0.025, was to be achieved. If the upper bound of the CI was ≤0.4%, noninferiority was concluded.

Three supportive analyses were done to support the primary analysis. In these analyses, the change from baseline in HbA_{1c} at week 26 was analyzed using the MMRM model as described above, but (1) missing data were not explicitly imputed; (2) data were analyzed by excluding HbA_{1c} data after hyperglycemia rescue and discontinuation from study treatment; and (3) analyses included only the per protocol population (all randomized participants who completed study procedures through week 26 and were compliant with the protocol).

The secondary endpoints, FPG and HbA_{1c} change from baseline by visit, were analyzed using the same or a similar (ie, FPG replaced HbA_{1c}) MMRM model as for the primary efficacy analysis in the model without imputation.

Safety data, including immunogenicity results, were listed and summarized by treatment group. Hypoglycemic events were classified as severe, documented symptomatic, asymptomatic, probable symptomatic, and pseudo hypoglycemia, and were analyzed separately from other AEs.

3. Results

3.1. *Participant disposition and characteristics*

A total of 624 patients were screened; of these, 316 patients were classed as screen failures (295 did not meet inclusion/exclusion criteria, 10 were lost to follow-up, and 11 were withdrawals by subject or physician decision), 308 patients were randomized, and 307 received at least 1 dose of study drug and were included in the intent-to-treat population. The most common reasons for withdrawal from the randomized study or treatment were "lost to follow-up" and "withdrew consent" (Table 1, Supplemental Fig. S2).

Of those participants who completed the randomized study, 8 were enrolled in the open-label extension study to receive additional treatment with the liquid albiglutide drug product prior to termination of this study. Results for these 8 patients are reported in Supplemental Table S1.

In the randomized trial, demographic and baseline characteristics were generally similar between treatment groups (Table 2). However, there were slightly more patients in the albiglutide liquid drug product group who had a baseline $HbA_{1c} \geq 8.0\%$ (64 mmol/mol) than in the lyophilized drug group (55.6% [85/153] vs 45.5% [70/154).

3.2. *HbA_{1c}*

In the randomized trial in both treatment groups, HbA_{1c} decreased from baseline to week 12 and this decrease was maintained through week 26 (Fig. 1a). The magnitude of the decrease in HbA_{1c} was similar between treatment groups. For the primary endpoint assessment (using imputed values for missing data and adjusting for baseline HbA_{1c}), the model-adjusted LS mean change in HbA_{1c} from baseline at week 26 was −1.1% (12 mmol/mol) in the albiglutide liquid group and −1.2% (13 mmol/mol) in the albiglutide lyophilized group (Table 3). The model-adjusted treatment difference between the two albiglutide products was 0.06% (95% CI: −0.13, 0.24 or −0.7 mmol/mol [95% CI: −1.4, 2.6]; $P = 0.0002$). Because the upper boundary of the 95% CI is <0.4% (<4.4 mmol/mol), these results establish noninferiority between the albiglutide liquid and albiglutide lyophilized drug products in patients with T2DM after repeat dosing.

The results of the 3 supporting analyses also demonstrated the noninferiority of the albiglutide liquid to the albiglutide lyophilized product (Table 3). The model-adjusted LS mean change in HbA_{1c} from baseline at week 26 for the models where (1) missing data were not explicitly imputed, (2) data after hyperglycemia rescue and study treatment discontinuation were excluded without imputations, and (3) included only the per protocol population without imputations were −1.2% (−13 mmol/mol), −1.1% (12 mmol/mol), and −1.2% (−13 mmol/mol), respectively, in the albiglutide liquid group and −1.2% (−13 mmol/mol), −1.2% (−13 mmol/mol), and −1.2% (−13 mmol/mol), respectively, in the albiglutide lyophilized group. The model-adjusted treatment differences were 0.01% (95% CI: −0.17, 0.20 or 0.1 mmol/mol [95% CI: −1.9, 2.2]; $P < 0.0001$), 0.06% (95% CI: −0.13, 0.26 or 0.7 mmol/mol [95% CI: −1.4, 2.8]; $P = 0.0005$), and −0.01% (95% CI: −0.20, 0.18 or 0.1 mmol/mol [95% CI: −2.2, 2.0]; $P < 0.0001$) for the 3 models, respectively.

In a subgroup analysis, we compared the 2 treatments in patients with baseline $HbA_{1c} \geq 8.0\%$ and those with baseline $HbA_{1c} < 8.0\%$. In patients with baseline $HbA_{1c} \geq 8.0\%$, the model-adjusted LS mean change in HbA_{1c} from baseline at week 26 in the albiglutide liquid group (n = 85) and the albiglutide lyophilized group (n = 70) was −1.4% (−15.3 mmol/mol) and −1.7% (−18.6 mmol/mol), respectively. The model-adjusted treatment difference between the two albiglutide products was 0.2% (95% CI: −0.04, 0.51 or 2.2 mmol/mol [95% CI: −0.44, 5.57]; noninferiority $P = 0.1193$).

Table 1 – Patient disposition for the randomized population.

	Albiglutide liquid, n (%)	Albiglutide lyophilized, n (%)	Total, n (%)
All randomized population	154	154	308
ITT population[a]	153 (99.4)	154 (100)	307 (99.7)
Safety population	153 (99.4)	154 (100)	307 (99.7)
Per-protocol population	124 (80.5)	128 (83.1)	252 (81.8)
PK population	151 (98.1)	149 (96.8)	300 (97.4)
Completed the study	138 (89.6)	140 (90.9)	278 (90.3)
Continued into the open-label extension study[b]	6 (3.9)	2 (1.3)	8 (2.6)
Completed the active treatment period but did not complete the follow-up period	1 (0.6)	1 (0.6)	2 (0.6)
Discontinued study treatment before the scheduled end of the treatment period	22 (14.3)	20 (13.0)	42 (13.6)
Withdrawn from the study	16 (10.4)	14 (9.1)	30 (9.7)
Reasons for patient withdrawal from the study			
Lost to follow-up	5 (3.2)	6 (3.9)	11 (3.6)
Withdrew consent	6 (3.9)	5 (3.2)	11 (3.6)
AE	3 (1.9)	2 (1.3)	5 (1.6)
Investigator discretion	2 (1.3)	1 (0.6)	3 (1.0)
Reason for discontinuing study treatment			
AE	8 (5.2)	5 (3.2)	13 (4.2)
Withdrew consent	7 (4.5)	6 (3.9)	13 (4.2)
Lost to follow-up	4 (2.6)	5 (3.2)	9 (2.9)
Protocol deviation	3 (1.9)	3 (1.9)	6 (1.9)
Investigator discretion	0	1 (0.6)	1 (0.3)

AE, adverse event; ITT, intent-to-treat; PK, pharmacokinetic.

[a] ITT population included all randomized patients who received at least 1 dose of study treatment and who had a baseline assessment.

[b] The open-label extension study (NCT02750930) was terminated on November 2, 2016, <4 weeks after the first patient was enrolled in the randomized study (October 7, 2016). The decision to terminate the extension study was a reflection of GlaxoSmithKline's decision to stop commercialization of albiglutide and not due to quality, safety, or efficacy concerns with the albiglutide liquid auto-injector or issues connected with the conduct of the study at any site.

Table 2 – Baseline characteristics and demographics (randomized study, safety population[a]).

	Albiglutide liquid (N = 153)	Albiglutide lyophilized (N = 154)	Total (N = 307)
Age in years, mean (SD)	57.6 (9.3)	56.6 (10.1)	57.1 (9.7)
Age category, n (%)			
<65 years	119 (77.8)	120 (77.9)	239 (77.9)
≥65 years	34 (22.2)	34 (22.1)	68 (22.1)
Females, n (%)	70 (45.8)	79 (51.3)	149 (48.5)
BMI (kg/m^2), mean (SD)	31.9 (5.0)	32.5 (4.6)	32.2 (4.8)
Ethnicity, n (%)			
Hispanic or Latino	59 (38.6)	62 (40.3)	121 (39.4)
Race, n (%)			
Asian	3 (2.0)	2 (1.3)	5 (1.6)
Black or African American	15 (9.8)	24 (15.6)	39 (12.7)
White	129 (84.3)	122 (79.2)	251 (81.8)
Other[b]	6 (3.9)	6 (3.9)	12 (3.9)
Duration of T2DM (years), mean (SD)	9.2 (7.0)	9.4 (7.1)	9.3 (7.1)
Baseline HbA_{1c}, mean (SD)			
%	8.14 (0.88)	7.99 (0.81)	8.06 (0.85)
mmol/mol	65 (10)	64 (9)	65 (9)
Baseline HbA_{1c} <8.0%/64 mmol/mol, n (%)	68 (44.4)	84 (54.5)	152 (49.5)
Baseline HbA_{1c} ≥8.0%/64 mmol/mol, n (%)	85 (55.6)	70 (45.5)	155 (50.5)
Background antidiabetic therapy, n (%)			
Stable dose of metformin	130 (85.0)	131 (85.1)	261 (85.0)
Diet and exercise	23 (15.0)	23 (14.9)	46 (15.0)

BMI, body mass index; HbA_{1c}, glycated hemoglobin; SD, standard deviation; T2DM, type 2 diabetes mellitus.

[a] Safety population included all enrolled participants who received at least 1 dose of study drug.

[b] Other category includes Native American or Alaskan native, native Hawaiian or other Pacific Islanders, and mixed.

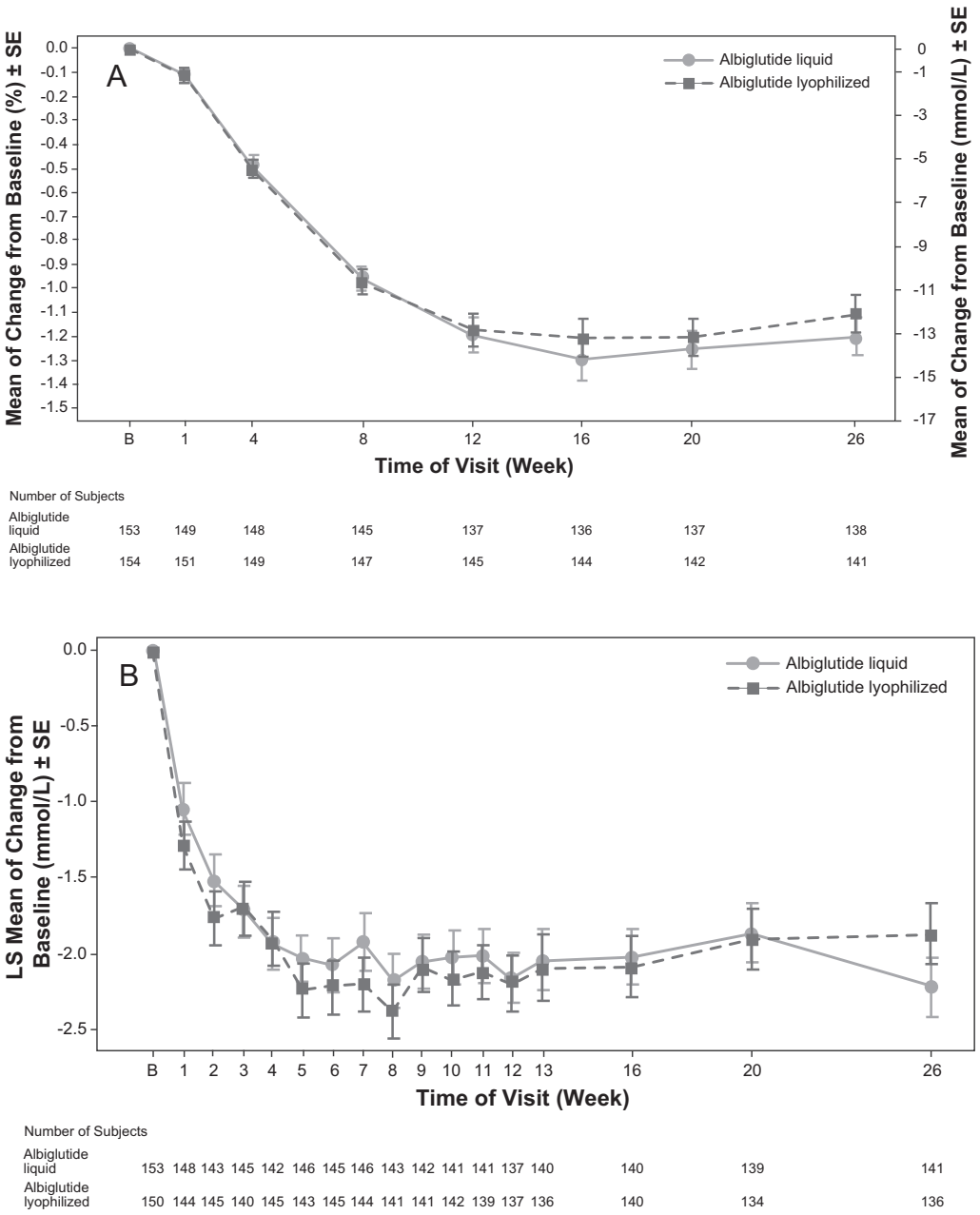

Fig. 1 – Change from baseline in (A) HbA_{1c} and (B) fasting plasma glucose over time (randomized study, ITT population).

In patients with baseline HbA_{1c} <8.0%, the model-adjusted LS mean change in HbA_{1c} from baseline at week 26 in the albiglutide liquid group (n = 68) and the albiglutide lyophilized group (n = 84) was – 0.8% (–8.7 mmol/mol) and –0.7% (–7.7 mmol/mol), respectively. The model-adjusted treatment difference between the two albiglutide products was –0.1% (95% CI: –0.40, 0.15 or –1.1 mmol/mol [95% CI: –4.37, 1.64]; noninferiority $P < 0.0001$).

3.3. *Fasting plasma glucose*

In both treatment groups, FPG decreased from baseline to week 5 and this decrease was maintained through week 26 (Fig. 1b). The model-adjusted LS mean change in FPG from baseline at week 26 was –2.22 mmol/L in the albiglutide liquid group and –1.88 mmol/L in the albiglutide lyophilized group (Table 3). The model-adjusted LS mean treatment difference between the 2 albiglutide products was –0.34 mmol/L (95% CI: –0.83, 0.14) demonstrating no difference between albiglutide liquid and albiglutide lyophilized drug products.

3.4. *Body weight*

In both treatment groups, reductions in body weight were observed at week 4 with a mean (SD) weight reduction of –0.26 (2.059) kg in the albiglutide liquid group and –0.31 (1.691) kg in the albiglutide lyophilized group. At week 26, the mean (SD) change from baseline in body weight was

Table 3 – Analysis of change from baseline in HbA_{1c} (%) (primary analysis with imputation) and fasting plasma glucose at week 26 (randomized study, ITT population[a]).

	Albiglutide liquid (N = 153)	Albiglutide lyophilized (N = 154)
HbA_{1c}		
Change from baseline, mean (SD)		
%	−1.13 (0.91)	−1.12 (0.93)
mmol/mol	−12 (10)	−12 (10)
Patients with missing HbA_{1c} at week 26, n	15	13
Model-adjusted change from baseline		
LS mean (SE), [95% CI][b]	−1.12 (0.07)	−1.18 (0.07)
%	[−1.26, −0.98]	[−1.32, −1.04]
mmol/mol	−12 (1) [−14, −11]	−13 (1) [−14, −11]
Difference from albiglutide lyophilized arm[b]		
Difference of LS means, [95% CI]		
%	0.06 [−0.13, 0.24]	
mmol/mol	0.7 [−1.4, 2.6]	
Noninferiority P[c]	0.0002	
FPG (mmol/L), n	141	136
Change from baseline, mean, (SD)	−2.23 (2.79)	−1.67 (2.98)
Model-adjusted change from baseline, LS mean (SE), [95% CI][d]	−2.22 (0.19) [−2.59, −1.84]	−1.88 (0.20) [−2.26, −1.49]
Difference of LS means from albiglutide Lyophilized arm [95% CI][d]	−0.34 [−0.83, 0.14]	

FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; ITT, intent-to-treat; LS, least squares; MMRM, mixed-effect model with repeated measures; SD, standard deviation, SE, standard error.

[a] ITT population included all randomized patients who received at least 1 dose of study treatment and who had a baseline assessment.

[b] Multiple imputations were used to replace missing data for change from baseline of HbA_{1c} at week 26 in both treatment arms as a first step then to make all the imputed values for the liquid drug product arm worse by the noninferiority margin of 0.4%.

[c] P values were from a one-sided t test to test whether the difference of LS means (albiglutide liquid – lyophilized) is equal to the prespecified noninferiority margin of 0.4%, and was estimated by combining the multiple sets of MMRM results.

[d] Based on MMRM model: Change = baseline FPG + treatment + region + age category + weight category + background antidiabetic therapy + visit week + treatment-by-visit week interaction. The MMRM model uses all available data after hyperglycemia rescue and discontinuation from investigational product. No explicit data imputation will be performed. Difference of least squares means (albiglutide liquid - albiglutide lyophilized) is estimated from the MMRM model.

−0.4 (3.975) kg in the albiglutide liquid group and −0.89 (3.654) kg in the albiglutide lyophilized group. Change in body weight was not a study endpoint, therefore, statistical significance was not calculated.

3.5. *Adverse events*

3.5.1. *Overall adverse events*

The percentage of patients reporting any AE was 67.3% and 61.7% in the albiglutide liquid and lyophilized groups, and 64.1% and 53.9% of the AEs were mild or moderate in intensity, respectively (Table 4). A higher percentage of patients receiving the albiglutide lyophilized product experienced nausea (16.2% vs. 11.1%), upper respiratory tract infection (13.0% vs. 5.2%), and injection-site erythema (4.5% vs. 0.7%). A higher percentage of patients receiving the albiglutide liquid product reported constipation (8.5% vs. 1.3%).

Six patients in the albiglutide liquid group and 5 from the albiglutide lyophilized group withdrew from treatment and 3 patients in the albiglutide liquid group and 2 from the albiglutide lyophilized group withdrew from the study due to AEs (Table 4). Except for ISR in the albiglutide liquid group (2 patients), no AE leading to study withdrawal was reported by more than 1 patient in any treatment group.

There were no deaths during the study, and serious adverse events (SAEs) occurred in 8 (5.2%) and 11 patients (7.1%) in the albiglutide liquid and lyophilized groups, respectively (Table 4). Only 2 SAEs reported by 1 patient in the albiglutide lyophilized group were considered related to treatment (pancreatitis acute and cholelithiasis). A blinded pancreatic adjudication committee positively adjudicated the acute pancreatitis, and the patient was withdrawn from study treatment.

3.5.2. *Adverse events of special interest*

ISRs were reported in 17 (11.1%) and 18 (11.7%) patients in the albiglutide liquid and lyophilized drug product groups, respectively. Most were mild in severity, none were severe, and none were reported as SAEs. The number and density of ISRs was greater in the albiglutide lyophilized group (24 events/30.7 patient-years [PY] vs 65 events/82.0 PY in the liquid and lyophilized groups, respectively) but the mean duration of an ISR event was higher in the albiglutide liquid group (19.5 days) compared with the albiglutide lyophilized group (8.8 days).

The number of patients reporting on-therapy hypoglycemic events (4 [2.6%] vs 9 [5.8%] in the liquid and lyophilized groups, respectively) was low. No on-therapy

Table 4 – Overview of adverse events (randomized study, safety population[a]).

	Albiglutide liquid (N = 153)		Albiglutide lyophilized (N = 154)	
	n %	Events (n)/AE Density (PY)	n %	Events (n)/AE Density (PY)
Any AE	103 (67.3)	362	95 (61.7)	483
Any SAE	8 (5.2)	10	11 (7.1)	13
Treatment-related SAE	0	0	1 (0.6)	2
Treatment-related AE	35 (22.9)	100	40 (26.0)	152
AE leading to treatment and/or study withdrawal	8 (5.2)	8	5 (3.2)	6
Any AE by maximum intensity				
Mild	52 (34.0)	260	38 (24.7)	342
Moderate	46 (30.1)	95	45 (29.2)	118
Severe	5 (3.3)	7	12 (7.8)	23
Any on-therapy AE	103 (67.3)	327/418.9	94 (61.0)	461/581.7
On-therapy AEs in >4% of patients				
Nausea	17 (11.1)	34/43.6	25 (16.2)	33/41.6
Injection site reaction	17 (11.1)	24/30.7	18 (11.7)	65/82.0
URTI	8 (5.2)	12/15.4	20 (13.0)	21/26.5
Diarrhea	15 (9.8)	17/21.8	11 (7.1)	21/26.5
Headache	12 (7.8)	18/23.1	14 (9.1)	16/20.2
Viral URTI	10 (6.5)	11/14.1	10 (6.5)	12/15.1
Constipation	13 (8.5)	13/16.7	2 (1.3)	2/2.5
Hypertension	8 (5.2)	8/10.3	7 (4.5)	7/8.8
Injection-site erythema	1 (0.7)	1/1.3	7 (4.5)	9/11.34

AE, adverse event; PY, patient-year; SAE, serious adverse event; URTI, upper respiratory tract infection.
[a] Safety population included all enrolled participants who received at least 1 dose of study treatment.

hypoglycemic event was recorded as an SAE or as severe in intensity.

Gastrointestinal events were reported in 46 patients (30.1%) in the albiglutide liquid group and 47 (30.5%) in the lyophilized group. One patient had a gastrointestinal event that was an SAE, and most events were considered to be related to the study drugs. Two patients in the albiglutide liquid group and 4 patients in the lyophilized group reported a gastrointestinal event that resulted in treatment or study withdrawal.

One patient in the albiglutide liquid group reported an on-therapy AE of papillary thyroid cancer. This AE was assessed as mild in intensity, not related to study medication, and did not result in study or treatment withdrawal.

3.6. *Immunogenicity*

Seventeen patients (11.2%) treated with the albiglutide liquid product and 16 (10.5%) treated with the lyophilized product tested positive for anti-albiglutide antibodies. Two patients in the albiglutide lyophilized group were positive at baseline. Of patients who tested positive, 13 (8.6%) and 11 (7.2%), respectively, also tested positive for anti- GLP-1 antibodies. No patient who tested positive for anti-albiglutide antibodies tested positive for anti-albiglutide neutralizing antibodies.

The number of patients who tested positive for anti-albiglutide antibodies increased during treatment with both albiglutide liquid and lyophilized albiglutide, but the increase was transient; the number of patients testing positive for anti-albiglutide antibodies was dramatically reduced at the 8-week follow up visit.

Of the 17 subjects in the albiglutide liquid group who experienced at least 1 ISR, 3 also tested positive for anti-albiglutide antibodies. Of the 18 subjects in the albiglutide lyophilized group who experienced at least 1 ISR, 6 subjects tested positive for anti-albiglutide antibodies.

3.7. *Pharmacokinetics*

Albiglutide plasma concentrations were similar for both the liquid and lyophilized treatment groups (Supplementary Table S2).

4. Discussion

The albiglutide liquid drug product was noninferior to the albiglutide lyophilized drug product in patients with T2DM; both products were equally effective in lowering HbA_{1c} and FPG levels. These results are consistent with previous studies of the effects of albiglutide in similar patient populations [3,5,6,9,10]. The observed efficacy on HbA_{1c} control in both treatment groups was consistent with glycemic control achieved at 32 weeks in the HARMONY 7 study, where model-adjusted change in HbA_{1c} from baseline to week 32 was −0.78% (95% CI −0·87 to −0·69) in the albiglutide group [10]. In an integrated analysis of five albiglutide phase 3 clinical trials, long-term HbA_{1c} reductions ranged from −0.29% [0.11] to −0.92% [0.13] [3]. The lowering of HbA_{1c} and FPG was also comparable with the HARMONY 2 study in which albiglutide (30 mg and 50 mg) was compared with placebo, and with the HARMONY 3 study in which albiglutide 30 mg was compared with placebo, sitagliptin (100 mg), and glime-

piride (2 mg). Both these studies were conducted in patients with T2DM inadequately controlled by diet and exercise, with or without metformin [5,7].

In general, the incidence and types of AEs reported were similar between patients treated with the albiglutide liquid and lyophilized products. The number and density of ISRs were higher in patients treated with the albiglutide lyophilized product compared with those treated with the albiglutide liquid drug product. This was mainly due to the higher number of injections site events (e.g., ISR, erythema, bruising, pruritus) in the albiglutide lyophilized group. Differences in PH, injection volume, and injection device could theoretically contribute to the difference in ISRs. There were also more severe AEs in the lyophilized group (7.8% vs 3.3%); however, both arms were below the range observed in an integrated analysis of safety of the albiglutide program, where the frequency was 14.8% for albiglutide, and 14.0% for all comparators [11]. Overall there were few differences in "on-therapy adverse events" between the 2 treatment groups, with constipation being more frequent in the liquid arm, and injection site erythemas more frequent in the lyophilized arm. The observed values were consistent with previously reported data. Across the albiglutide clinical program constipation was observed in 5.2% of the cases [12]. In an integrated analysis of safety of albiglutide trials, injection-site reactions were observed in 9.0% vs 2.0% of patients for albiglutide vs. all comparators, and injection-site erythema in 2.0% vs 0.5% of patients in albiglutide vs. all comparators, respectively [11].

The lyophilized formulation of albiglutide is provided as a single-dose pen injector that requires reconstitution by the patient before use. A liquid formulation of albiglutide in a single dose, ready-to-use prefilled auto-injector syringe may prove more convenient for patients and thereby has the potential to improve adherence. However, since the study design regarding drug administration in this study did not reflect real-world use the potential for albiglutide liquid formulation to improve patient adherence requires additional study.

Limitations of the randomized study include the 26-week treatment duration, which was relatively short for patients with T2DM, and may have limited the ability to observe AEs that could appear over a longer period. A 26-week extension study to assess safety over a longer period was terminated early by the sponsor, who decided to stop commercialization of albiglutide. As only 8 patients had enrolled in the extension study before it was terminated, no conclusions regarding the longer-term safety of albiglutide liquid product can be made based on the limited data. Another limitation was the omission of a placebo arm in the randomized study in order to determine the effects of active treatment in both treatment groups. Additionally, the requirement for 2 separate injections each week during the randomized trial, as well as drug administration by the study site rather than by the individual patients, does not reflect real-world use. Therefore, these patients, who were unaccustomed to injectable treatments, may have reported additional or different incidence of AEs if they had self-administered a single drug.

In conclusion, the albiglutide liquid drug product demonstrated noninferiority to the albiglutide lyophilized drug product, and both products were highly effective in lowering HbA_{1c} and FPG. Additionally, the incidence and types of AEs reported with the albiglutide 50-mg liquid drug product was consistent with the known profile for the albiglutide 50-mg lyophilized drug product, and no new safety signals were identified in the study.

5. Data sharing statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Author contributions

BCS, MS, and CW contributed to the conception or design of the study and the data analysis or interpretation of the study. JS and GV contributed to the data analysis or interpretation of the study. AN contributed to the conception or design of the study. All authors provided critical review and final approval of the manuscript for publication and agree to take responsibility for the content.

Conflict of interest disclosure

BCS, JS, GV, MS, CW, and AN are employees of and hold equity stock in GlaxoSmithKline.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.04.018.

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