Randomized 52-week Phase 2 Trial of Albiglutide Versus Placebo in Adult Patients With Newly Diagnosed Type 1 Diabetes

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Clinical Trial Information: This study is based on data from NCT02284009 (registered at ClinicalTrials.gov)

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Disclosure Summary

PP received grant support from AstraZeneca, Eli Lily, GlaxoSmithKline (GSK), Medtronic, and Sanofi; and received personal fees from Eli Lily, GSK, and Sanofi. EB received advisory board or speaker fees from Abbott, AstraZeneca, Medtronic, Novartis, Roche, Sanofi, and Takeda. NL has nothing to disclose. FT has participated in speaker's bureau and received consultant/advisory board fees from AstraZeneca, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GSK, Janssen Pharmaceuticals, Merck Sharpe & Dohme, Novartis Pharmaceuticals Co., Novo Nordisk, Sanofi, and Regeneron Pharmaceuticals. M-C V has received fees to the hospital for the trial from GSK, A-G Z has nothing to disclose. DC, JH, GV, and SJ are employees of and own stock in GSK.

Abstract

Context: GLP-1 receptor agonists are an established therapy in patients with type 2 diabetes; however, their role in type 1 diabetes remains to be determined.

Objective: Determine efficacy and safety of once-weekly albiglutide 30mg (up-titration to 50mg at week 6) versus placebo together with insulin in patients with new-onset type 1 diabetes and residual insulin production.

Design: 52-week, randomized, phase 2 study (NCT02284009).

Methods: A prespecified Bayesian approach, incorporating placebo data from a prior study, allowed for 3:1 (albiglutide:placebo) randomization. The primary endpoint was 52-week change from baseline in mixed meal tolerance test (MMTT) stimulated 2-hour plasma C-peptide area under the curve (AUC). Secondary endpoints included metabolic measures and pharmacokinetics of albiglutide.

Results: 12/17 (70.6%, placebo) and 40/50 (80.0%, albiglutide) patients completed the study. Within our study, mean (SD) change from baseline to week 52 in MMTT-stimulated 2-hour plasma C-peptide AUC was −0.16 nmol/L (0.366) with placebo and −0.13 nmol/L (0.244) with albiglutide. For the primary Bayesian analysis (including prior study data) the posterior treatment difference (95% credible interval) was estimated at 0.12 nmol/L (0–0.24);the probability of a difference ≥0.2 nmol/L between treatments was low (0.097). A transient significant difference in maximum C-peptide was seen at week 28. Otherwise, no significant secondary endpoint differences were noted. **.** On-therapy adverse events were reported in 82.0% (albiglutide) and 76.5% (placebo) of patients.

Conclusion: In newly diagnosed patients with type 1 diabetes, albiglutide 30−50 mg weekly for 1 year had no appreciable effect on preserving residual β-cell function versus placebo.

Keywords: Type 1 diabetes mellitus, albiglutide, GLP-1 receptor agonist, insulin

Précis: Patients with new onset type 1 diabetes were treated with albiglutide for 1 year. No significant effect on glycemic or metabolic parameters was observed. No new safety signals were noted.

Introduction

Type 1 diabetes is a destructive autoimmune disease affecting pancreatic islet β-cells. Patients with type 1 diabetes progressively lose β-cell function, resulting in lifelong dependence on insulin. At clinical onset, some insulin secretory capacity is retained (1; 2). Since retention of β-cell function is associated with improved glycemic control and a reduced risk of hypoglycemia and end-organ diabetic complications, preserving β-cell function has become a therapeutic target of interventions (2-4). Interventional strategies, mainly immune-modifying therapies, aimed at abrogating β-cell destruction have been examined for preventing or reversing the natural course of disease, but none have shown a sustained benefit in retention of insulin production (preserving β-cell function) after a clinical diagnosis (5). A combination approach that includes immune-modifying agents, insulin, and β-cell stimulatory agents has the potential to abrogate the type 1 diabetes disease process more successfully than single agents (6).

The incretin glucagon-like peptide-1 (GLP-1) is a hormone secreted from intestinal entero-endocrine cells that regulates islet cell function, potentiates insulin secretion, and inhibits glucagon secretion after a meal (7). In animal models of diabetes, GLP-1 promotes β-cell growth and survival and increases β-cell mass (7). These actions spurred the development of GLP-1–based therapeutics, and GLP-1 receptor agonists (GLP-1 RAs) are now an established class of agents for treatment of type 2 diabetes (8; 9).

The GLP-1 RA liraglutide has been investigated as an adjunct to insulin for improving glycemic control in patients with type 1 diabetes of varying duration. The addition of liraglutide resulted in better glycemic control, reduced insulin requirement,

and some degree of body weight loss, but increased rates of hypoglycemia and hyperglycemia with ketosis were observed. GLP-1 RAs are not licensed for use in type 1 diabetes (10; 11).

Despite the limitations of use as adjunctive therapy uncovered in clinical trials, GLP-1 RAs may still have therapeutic potential in type 1 diabetes. *In vitro* and animal data have suggested that GLP-1 RAs are effective in maintaining and even expanding β-cell mass (7). Intervening with these agents at an early stage of type 1 diabetes, such as at clinical onset or even at the presymptomatic stage, may have beneficial effects in preserving β-cell mass (12). In the nonobese diabetic mouse model of autoimmune diabetes, GLP-1 RA enhanced β-cell recovery when administered with or without immune intervention (13; 14).

Albiglutide is a once-weekly, long-acting GLP-1 RA with demonstrated efficacy and safety in type 2 diabetes (15). It has been shown to reduce the risk of major adverse cardiovascular events in patients with established cardiovascular disease (16). This study examined the effect of albiglutide therapy on endogenous insulin secretion in patients with newly diagnosed type 1 diabetes.

Research Design and Methods

Objective

The primary study objective was to determine the effect of albiglutide versus placebo on endogenous insulin secretion, as measured by stimulated C-peptide, over 52 weeks when added to standard of care in patients with new-onset type 1 diabetes . The stimulated 2-hour C-peptide area under the curve (AUC) measured under standardized conditions following a mixed meal challenge is a sensitive, well-

accepted, and clinically validated measure of endogenous insulin secretion and β-cell function (2; 17). Key secondary objectives were to assess the effect of albiglutide versus placebo on plasma glucagon concentration, glycemic control and variability, daily insulin requirement, body weight, and glycosylated hemoglobin A_{1c} (HbA_{1c}) responder and partial remission rates and to evaluate tolerability and safety, including hypoglycemia.

Study Design and Participants

This was a 52-week, phase 2, randomized, placebo-controlled, parallel group, double-blind, multicenter study in patients with newly diagnosed type 1 diabetes and residual insulin production. The study was conducted at 29 sites in Europe (Spain 10, United Kingdom 9, Germany 4, France 3, and Italy 3) and consisted of an 8-week screening period, 52-week treatment period, and 12-week follow-up period (Figure 1).

The study enrolled patients aged 18 to 30 years with body mass index (BMI) ≤32.0 kg/m^2 (to avoid inclusion of patients with type 2 diabetes) and newly diagnosed type 1 diabetes (4–8 weeks between diagnosis, defined as first insulin administration, and administration of the first dose of study drug). All patients received background insulin therapy or had required insulin therapy for ≥7 days from diagnosis and had residual pancreatic β-cell function as measured by a peak stimulated C-peptide level >0.20 nmol/L during the screening mixed meal tolerance test (MMTT) when fasting blood glucose levels were >70 mg/dL and ≤200 mg/dL (>3.9 mmol/L and ≤11.1 mmol/L). Only patients using basal bolus insulin were eligible; all other insulin regimens and noninsulin antihyperglycemic therapies were disallowed. Additionally,

patients had to test positive for ≥1 autoantibody typically associated with type 1 diabetes including antiglutamic acid decarboxylase, antityrosine phosphatase-like protein IA-2, or insulin autoantibody. All patients who agreed to participate in the study provided written informed consent.

Patients in the current study were randomized in a 3:1 ratio to receive albiglutide 30 mg once weekly (increasing to 50 mg at week 6 if the 30-mg dose was tolerated) or placebo once weekly. Historical placebo data from the DEFEND-1 study was incorporated into the current placebo group for the primary efficacy analysis. Albiglutide dose was derived from dosing studies for blood glucose lowering in an adult T2DM population (over a range of bodyweight), which overlaps with respect to body weight with that of the adult T1DM population. The dose in T1DM participants was to be up titrated from 30 mg to 50 mg, if the starting dose was tolerated, to ensure that the clinical exposures in albiglutide patients would be well within the therapeutic range and hence to maximise the chance of observing a treatment effect. Randomized treatment assignment was made via an interactive voice response system and was based on a sequestered fixed randomization schedule. Once a patient met eligibility criteria, study center personnel called the interactive voice response system to execute each randomization. Study treatment with albiglutide was blinded to patients, study personnel, and sponsor; doses of placebo matching those for albiglutide were used to preserve blinding. A treatment assignment could be unblinded in the case of an emergency or in the event of a serious adverse event (SAE).

Albiglutide or matching placebo was administered by subcutaneous injection (abdomen, thigh, or upper arm). Patients received insulin as prescribed by the investigator throughout the study (screening to follow-up visit). To ensure that C-peptide changes over time were not confounded by suboptimal glycemia, basal and mealtime insulin doses were titrated according to protocol-defined algorithms (Tables 1 and 2) and were based on self-measured plasma glucose profiles.

The study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP), all applicable patient privacy requirements, and the ethical principles outlined in the Declaration of Helsinki 2008. The study was approved by a national, regional, or investigational center ethics committee and followed applicable country-specific requirements for constitution of independent ethics committees.

Assessments

Efficacy assessments were made at baseline and at regular prespecified time points during treatment after the first dose and included plasma C-peptide AUC and maximum plasma concentration (weeks 16, 28, 52, and 64), plasma glucagon AUC (weeks 16, 28, 52, and 64), 72-hour blood continuous glucose monitoring (CGM) (weeks 28 and 52 only), and daily insulin use, HbA_{1c}, and body weight (weeks 4, 8, 16, 28, 40, 52, and 64).

To measure C-peptide and glucagon, all patients underwent an MMTT with a standardized amount of a nutritional drink (Ensure, 6 mL per kg body weight up to a

maximum of 360 mL). Blood samples were taken 10 minutes before time 0, immediately before (time 0), and at 15, 30, 60, 90, and 120 minutes after drinking, and the AUC was calculated. The mean daily insulin dose was calculated as the mean of the patient's daily insulin use over 3 consecutive days preceding a study visit. Weight-adjusted insulin dose was calculated as mean daily insulin units/kg/day (24-hour period). HbA_{1c} was recorded at regular visits. CGM was performed in the week prior to a visit after a patient was fitted with a CGM monitor. HbA_{1c} responders were defined as patients with HbA_{1c} ≤7.0% (53 mmol/mol) and insulin dose <0.5 units/kg/day. Partial remission was defined as insulin-dose adjusted HbA_{1c} (calculated as % HbA_{1c} + 4 x insulin dose [units/kg/24 hours]) ≤9.0% (11.7 mmol/mol) (18).

A population pharmacokinetic analysis was conducted to derive key pharmacokinetic parameters (clearance [CL/F], volume of distribution [V/F] and absorption rate [Ka]) of albiglutide in patients with type 1 diabetes. The analysis used a previous population pharmacokinetic model (19) in patients with type 2 diabetes that was developed as part of the clinical development program for albiglutide.
Compliance was assessed for albiglutide (and matching placebo) at each study visit after the baseline visit through the end-of-treatment visit (week 52) inclusive. Patients were instructed to return all unused and used injector pens at each visit (except for week 2 where only used injector pens were returned) for assessments of compliance.

Safety assessments included monitoring of adverse events (AEs), hypoglycemic and hyperglycemic events, clinical laboratory tests, vital signs, physical examination, and

electrocardiograms. Hypoglycemic events were classified as severe, documented symptomatic, asymptomatic, probable symptomatic, and pseudohypoglycemia (symptoms of hypoglycemia with plasma glucose concentration >70 mg/dL [>3.9 mmol/L] but approaching that level) based on published guidelines (20).

Statistical Analyses

The study planned to randomly assign 68 patients to albiglutide or placebo using a 3:1 ratio and assumed a 10% drop-out rate. Due to anticipated recruitment challenges, the study was specifically designed to reduce the number of required placebo-treated patients by utilizing a 3:1 (albiglutide:placebo) randomization ratio and a prospectively defined Bayesian analysis method which incorporated historical data from 53 age-matched (ie, aged 18–30) placebo-treated patients from the DEFEND-1 study (21) in addition to the patients allocated to placebo in this study to increase the practicability and efficiency of the trial (ie, reduced sample size and increased precision of treatment estimates). DEFEND-1 had similar inclusion and exclusion criteria and a 52-week primary endpoint (with collection of stimulated C-peptide data). Sample size calculations took into account historical data from the 53 placebo-treated patients in the DEFEND-1 study (21) and used a Bayesian approach for power and minimal treatment difference evaluation. Power was calculated for the primary efficacy analysis. Depending on the degree to which historical data contribute to the placebo result of the current trial, at a 2-sided significance level of 0.05, a sample size of 60 evaluable patients (45 albiglutide, 15 placebo) provides 90% power to detect a treatment effect ranging from 0.19 nmol/L (using information from all 53 patients in DEFEND-1) to 0.30 nmol/L (not using any historical data).

The intent-to-treat population consisted of all randomized patients who received at least 1 dose of study medication and who had at least 1 postbaseline assessment for the primary endpoint. The safety population consisted of all patients who received at least 1 dose of study medication.

The primary efficacy endpoint was the change from baseline in 2-hour MMTT plasma C-peptide AUC at week 52. The primary analysis was performed using a Bayesian analysis incorporating historical placebo data from the DEFEND-1 study (21) using a robust mixture prior, which allowed weighting of the historical DEFEND-1 placebo data to depend on its similarity to the albiglutide study data (22). A model for change from baseline in 2-hour MMTT C-peptide AUC was used to estimate and compare the albiglutide and placebo treatment effects at week 52. To control for potential confounding variables for subjects enrolled in this study, a repeated-measures model was fitted with change from baseline 2-hour MMTT plasma C-peptide AUC as a dependent variable and baseline 2-hour MMTT C-peptide AUC, age, and treatment group-by-visit interaction as independent variables. An estimate of the posterior treatment difference from placebo and 95% credible interval was derived from the Bayesian analysis and the probability of treatment difference ≥0.2 nmol/L (clinically relevant effect), ≥0.1 nmol/L (some clinically relevant effect), or ≥0.0 nmol/L (no effect) was determined.

Secondary efficacy endpoints of change from baseline in maximum stimulated C-peptide, plasma glucagon, % HbA_{1c}, mean daily insulin use, body weight, and 72-hour CGM endpoints at week 52 were analyzed using a mixed model repeated-measures (MMRM) model. The percentage of HbA_{1c} responders and of patients

achieving partial remission were analyzed using a nonparametric, covariance-adjusted, extended Mantel-Haenszel test, adjusting for age category; the treatment group difference was presented as an odds ratio, together with associated 95% confidence interval (CI) and *P* value.

Safety data were listed and summarized by treatment group.

Results

Description of Patients

The study was conducted between October 10, 2014, and October 18, 2017. Because of slow recruitment, the study was stopped early after 67 of the planned 68 patients were enrolled. Of 89 patients screened, 67 were randomized to receive albiglutide (n = 50) or placebo (n = 17). Twelve patients in the placebo group (70.6%) and 40 in the albiglutide group (80.0%) completed the study. The main reasons for study withdrawal were loss to follow-up (placebo, 3; albiglutide, 5) and withdrawal by patient (placebo, 1; albiglutide, 5); 1 patient in the placebo group withdrew due to an AE. The intent-to-treatpopulation consisted of 15 patients in the placebo group (88.2%) and 46 in the albiglutide group (92.0%); excluded patients had no postbaseline assessment of the primary endpoint.

Forty-nine out of 50 patients completed week 6. Most albiglutide patients (45/49; 91.8%) received the 50-mg dose at weeks 6 and 41 (83.7%) remained on this dose for the duration of the study. Most patients were exposed to treatment (albiglutide 41/50 [82.0%] and placebo 12/17 [70.6%]) for >40 weeks. Mean overall treatment compliance was 97.8% in the placebo group and 98.3% in the albiglutide group.

Baseline demographic and clinical characteristics of the intent-to-treat population were similar between treatment groups (Table 3). The mean baseline HbA_{1c} was 7.27% (55.91 mmol/mol) and 7.30% (56.30 mmol/mol), the mean baseline C-peptide AUC was 0.59 nmol/L and 0.55 nmol/L, and mean body weight was 69.15 kg and 66.04 kg in the placebo and albiglutide groups, respectively. Overall, patients received their first dose of study drug within a mean of 52.3 days of diagnosis.

Primary Endpoint

The median and mean (SD) change from baseline to week 52 in MMTT-stimulated 2-hour plasma C-peptide AUC was similar between the placebo and albiglutide groups (median −0.14 nmol/L, mean −0.16 nmol/L [0.37] *vs.* median −0.12 nmol/L, mean −0.13 nmol/L [0.24]) (Table 4) in the current study. In the historical placebo group from the DEFEND-1 study, the mean change was −0.27, suggesting that the assumption that this placebo group was similar to that of the current trial might not hold true, and raising the question of the appropriateness of the Bayesian approach under the chosen robust mixture prior. For the primary Bayesian analysis, incorporating and assigning 50% weight to historical placebo data from DEFEND-1, the posterior treatment difference (95% credible interval) was estimated to be 0.12 nmol/L (0–0.24). The probability of a treatment difference ≥0.2 nmol/L between albiglutide and placebo was low (0.097). Sensitivity analyses using 0% or 100% historical data confirmed the low probability of a treatment difference of ≥0.2 nmol/L (Table 5). Non-Bayesian sensitivity analysis of the primary endpoint that excluded the historical DEFEND-1 placebo data confirmed that there was no significant difference between the albiglutide and placebo groups at week 52 (Table 4).

Compared with the placebo group, mean (SD) C-peptide AUCs in the albiglutide group were similar at all time points albeit numerically higher at week 16 (0.63 [0.35] *vs.* 0.58 [0.38] nmol/L) and 28 (0.58 [0.37] *vs.* 0.46 [0.27] nmol/L), similar at week 52 (0.45 [0.32] *vs.* 0.46 [0.40] nmol/L), and numerically lower at week 64 (0.33 [0.24] *vs.* 0.40 [0.31] nmol/L) (Figure 2A).

Secondary Endpoints

Maximum C-peptide values at week 28 were statistically significantly greater in the albiglutide group (treatment difference for albiglutide *vs.* placebo was 0.27 nmol/L [95% CI, 0.08–0.45; *P* = 0.0051]) but this was not sustained to week 52 (Figure 2B).

At week 52, no statistically significant differences were noted between the albiglutide and placebo groups for change from baseline in plasma glucagon AUC, HbA_{1c}, mean daily insulin use/weight, time spent with plasma glucose levels ≤3.9, >3.9 to ≤10, or >10 mmol/L, or body weight (Table 4). Mean glucagon AUC values were generally numerically lower for albiglutide compared with placebo over the course of the study (Figure 2C). Reduction in HbA_{1c} was similar in both treatment groups throughout the study (Figure 3). Mean daily insulin use (units/kg/day), which was similar between the groups at baseline, was generally higher in the albiglutide group than in the placebo group from week 8 to week 64 (Figure 4). CGM over 72 hours revealed no differences between groups in change from baseline in time spent within 3 plasma glucose ranges. In both groups, time spent with plasma glucose ≤3.9 or >10.0 mmol/L was higher at week 52 than at baseline (Figure 5). Mean body weight in the albiglutide group remained steady to week 28 (mean [SD] change from

baseline: –0.18 [3.2] kg) and then increased slightly through week 64 (mean [SD] change from baseline: 1.63 [3.8] kg) (Figure 6). The placebo group showed weight loss from week 8 (mean [SD]: 70.08 [14.1] kg) to week 28 (mean [SD]: 66.08 [11.8]) then weight gain after week 40 (mean [SD]: 66.08 [11.3] kg) to week 64 (mean [SD]: 68.29 [11.5]; however, the mean weight at baseline was higher in the placebo group (69.2 vs 66.0 kg). The proportions of HbA_{1c} responders (HbA_{1c} ≤7% [53 mmol/mol] and mean daily insulin use <0.5 units/kg/day) and patients with partial remission status achieving insulin dose-adjusted HbA_{1c} ≤9% were also similar between the 2 groups at week 52 (Table 4).

Hypoglycemia

Significant hypoglycemia was recorded as severe, documented symptomatic, and asymptomatic in the intent-to-treat population. All patients reported at least 1 significant hypoglycemic event during the study. From baseline to ≤ week 24, 0/15 (0%) patients in the placebo group and 2/46 (4.3%) patients in the albiglutide group reported a severe hypoglycemic event; 12/15 (80%) patients in the placebo group and 43/46 (93.5%) patients in the albiglutide group reported a documented symptomatic hypoglycemic event; and 15/15 (100%) patients in the placebo group and 42/46 (91.3%) patients in the albiglutide group reported an asymptomatic hypoglycemic event. The number of severe, documented symptomatic, and asymptomatic hypoglycemic events, respectively, from week 24 to ≤ week 52 were 0/13 (0%) in the placebo group and 0/45 (0%) in the albiglutide group, 11/13 (84.6%) in the placebo group and 32/45 (71.1%) in the albiglutide group, and 10/13 (76.9%) in the placebo group and 36/45 (80.0%) in the albiglutide group.

Population Pharmacokinetics

The population pharmacokinetic analysis of albiglutide included 49 patients. The results showed that the final model was able to describe data in newly diagnosed type 1 diabetes with good precision. The population pharmacokinetic parameters of albiglutide in type 1 diabetes patients were 45.1 mL/h, 4830 mL, and 0.0122 h^{-1} for CL/F, V/F, and Ka respectively. Body weight and estimated glomerular filtration rate were significant covariates with respect to total clearance (CL/F).

Safety

An overview of AEs is provided in Table 6. More albiglutide-treated patients reported an on-therapy AE compared with placebo-treated patients (82% *vs.* 76%), with gastrointestinal AEs the most frequently reported on-therapy AEs in patients receiving albiglutide (Table 7), the latter being consistent with the known profile of albiglutide and other GLP-1 RAs when used in type 2 diabetes. On-therapy treatment-related AEs were twice as frequent among albiglutide patients (60%) than in the placebo group (29%), with the most frequent events being nausea (38% *vs.* 18%) and diarrhea (20% *vs.* 12%) (Table 6).

Two patients in the placebo group had on-therapy serious adverse events (SAEs) (urticaria and suicidal ideation), which resulted in discontinuation of study treatment. The urticaria was considered treatment related. In the albiglutide group, there was 1 on-therapy SAE—a case of uterine leiomyoma. It was not considered to be treatment related.

Hypoglycemia was also reported as an AE of special interest in the safety population (Table 6). No hypoglycemic event was recorded as an on-therapy SAE or resulted in treatment discontinuation or study withdrawal.

All injection-site reactions were reported in albiglutide-treated patients (14% *vs.* 0%). All events were mild or moderate in intensity. The majority were not considered related to study medication and all events resolved.

Discussion

To our knowledge, this is the largest study examining use of a long-acting GLP-1 RA in a well-characterized and homogeneous cohort of adult patients with newly diagnosed type 1 diabetes. The primary and key secondary efficacy endpoints failed to show any clinically or statistically significant treatment difference when comparing albiglutide with placebo over a period of 52 weeks. Differences between treatment groups with respect to change from baseline in C-peptide AUC did not reach the pre-defined level of 0.2 nmol/L (which defined a positive treatment difference for our study) whether historical placebo data from DEFEND-1 was included in or omitted from these analyses. Based on the known profile of albiglutide used for type 2 diabetes, no new safety signals were noted in the albiglutide group. Hypoglycemia, a well-documented side effect of insulin therapy, was similar in both treatment groups and was not affected by addition of albiglutide despite the apparently greater total daily dose of insulin used in albiglutide-treated patients.

The finding that C-peptide AUC was numerically higher at weeks 16 and 28 and that the maximum stimulated C-peptide level was significantly higher at week 28 in the

albiglutide versus the placebo group suggests that albiglutide may be capable of increasing β-cell function soon after diagnosis up to week 28. Although purely speculative, one possible explanation is that with intensive insulin treatment and consequent reduced β-cell glucotoxicity, a healthier β-cell may respond better to a meal stimulus following albiglutide treatment (23). With continuation of the autoimmune process over time, most β-cells are destroyed, which may explain why albiglutide is not effective over a longer period. However, autoantibodies were only measured at screening, to ensure specificity of diagnosing type 1 diabetes, and not during the study or study follow-up.

Both treatments were associated with lowering of HbA_{1c}. The change from baseline in HbA_{1c} was similar and virtually identical between the treatment groups throughout the study and CGM over 72 hours revealed no differences between groups. Mean daily insulin use (units/kg/day) was generally higher for albiglutide than placebo from week 8 through week 64 but did not reach statistical significance.

The pharmacokinetic analysis confirmed that exposure to albiglutide is dependent on body weight. A similar CL/F of 51.6 mL/hour was observed in a previous population pharmacokinetic analysis in Japanese patients with type 2 diabetes with similar mean body weight (70.5 kg *vs.* 66.04 kg in the present study) (19).

In patients with type 2 diabetes, GLP-1 RAs are commonly used in combination with insulin. The potential for GLP-1 RAs in lowering HbA_{1c}, promoting weight loss, reducing insulin doses, and lowering hypoglycemia risk in patients with type 1 diabetes has led to clinical trials of GLP-1 RAs in these patients. A meta-analysis of

GLP-1 RAs in patients with type 1 diabetes including studies of exenatide or liraglutide combined with insulin therapy found that GLP-1 RAs lowered HbA_{1c} and weight, and reduced insulin dose (24). However, 3 studies were <6 months in duration and 5 of 7 trials were in patients with a duration of diabetes >18 years, 1 study did not provide this information, and 1 study was in newly diagnosed patients. In the study in newly diagnosed patients, Kumar and colleagues assessed addition of exenatide or sitagliptin to insulin therapy in a 12-month, open-label trial, and found that the addition of either agent decreased insulin requirements but did not increase endogenous insulin (25).

Two randomized, placebo-controlled, double-blind studies, which were not included in the meta-analysis, assessed liraglutide in patients with type 1 diabetes (10; 11). In both studies, liraglutide added to insulin treatment resulted in modest dose-dependent reductions in HbA_{1c} together with a reduced total daily insulin requirement, but was accompanied by increased rates of hypoglycemia and hyperglycemia with ketosis. The effect of GLP-1 RAs in patients with established type 1 diabetes may be related to adjunctive benefit rather than an effect on the natural history of worsening β-cell reserve in new-onset type 1 diabetes, as evaluated in the current study. The difference in efficacy between GLP-1 RAs in type 1 diabetes could also be related to pharmacologic and/or pharmacokinetic differences.

Our study has limitations. The placebo group from DEFEND-1 was used in the primary Bayesian analysis to allow for a 3:1 randomization of albiglutide:placebo. DEFEND-1 was a randomized, placebo-controlled, double-blind, multicenter study comparing otelixizumab, a chimeric monoclonal antibody that targets the CD3/T-cell

receptor, with placebo in patients with newly diagnosed type 1 diabetes (21). The patient population (patients with newly diagnosed type 1 diabetes) and primary endpoint (change from baseline in 2-h C-peptide AUC from an MMTT at 52 weeks) were similar to those of the current trial. Differences between the placebo groups include slightly higher mean weight (72 kg *vs.* 69 kg) and BMI (23.5 kg/m^2 *vs.* 22.6 kg/m^2), which could be indicative of a more slowly evolving diabetes. Patients in the placebo group for DEFEND-1 also had a higher mean baseline C-peptide AUC compared with placebo patients in the current study (0.68 nmol/L vs 0.62 nmol/L), suggesting that the assumption that this placebo group was similar to that of the current trial might not hold true and raising the question of the utility of the Bayesian approach. In the non-Bayesian analysis (excluding the DEFEND-1 placebo data), the treatment difference was smaller (0.04 nmol/L) than the Bayesian analysis (including the DEFEND-1 placebo data) (0.12 nmol/L). In either case, the treatment differences did not reach the predefined level of 0.2nmol/L, which defined a positive treatment difference for our study. Therefore, the overall conclusion is not affected. The C-peptide level may be a narrow target for observing treatment differences, and a composite endpoint (ie, beta score including fasting blood glucose, stimulated C-peptide, HbA_{1c}, weight-adjusted daily insulin) may be more appropriate because C-peptide is influenced by the blood glucose level, creatinine level, and body weight (26). The placebo group may also have been too small to observe any between-group differences. Additional limitations include the high withdrawal rate observed in the study, likely due to its long duration and intensive intervention.

Conclusions

Albiglutide failed to show any clinically significant treatment difference compared with placebo for the primary and secondary efficacy endpoints in patients with newly diagnosed type 1 diabetes at one year. Albiglutide did not increase the risk of significant hypoglycemia, and no new safety signals were noted in patients with type 1 diabetes.

Acknowledgements

Funding for this study (NCT02284009 available from www.clinicaltrials.gov) was provided by GlaxoSmithKline (GSK). Editorial support (assembling tables and figures, collating author comments, copyediting, fact checking, and referencing; Meher Dustoor, PhD, Sarah Hummasti, PhD, and Nancy Price, PhD) and graphic services were provided by AOIC, LLC, and were funded by GSK. The authors wish to thank Jo Dole, PhD, of GSK, for her contributions to the early development of this manuscript.

Author Contributions

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. PP, EB, DC, M-CV, A-GZ, and SJ contributed to the conception or design of the study; PP, EB, JH, NL, FJT, M-CV, A-GZ, GV, and SJ contributed to the acquisition of the data and the data analysis and interpretation. All authors contributed to the writing, provided critical review, and gave final approval for publication and all authors take responsibility for its content, specifically Salim Janmohamed.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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

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Figure Legends

Figure 1. Study design.

[a]Albiglutide: start 30 mg once weekly, increase to 50 mg once week 6 if lower dose is tolerated.
[b]Insulin dose titration per protocol-defined algorithm.
NOT1DM, new-onset type 1 diabetes melitus.

Figure 2. C-peptide AUC (A) maximum stimulated C-peptide (B) and plasma glucagon AUC (C) over the duration of the study (intent-to-treat population).

(A)
P values from MMRM analysis of change from baseline in C-peptide AUC when comparing albiglutide to placebo were *P* = 0.3364 at week 16, *P* = 0.0286 at week 28, *P* = 0.6505 at week 52, and *P* = 0.6375 at week 64. *P* value is from a 2-sided t-test to test whether the difference of LS Means (albiglutide - placebo) is equal to zero.

AUC, area under the curve; B, baseline; LS, least square; MMRM, mixed model repeated measures; MMTT, mixed meal tolerance test; SE, standard error.

Note: Baseline is defined as the last nonmissing value with an assessment date on or before the first day of study medication.

(B)
P values from MMRM analysis of change from baseline in maximum stimulated C-peptide when comparing albiglutide to placebo were *P* = 0.0051 at week 28 and *P* = 0.3571 at week 52. *P* value is from a 2-sided t-test to test whether the difference of LS Means (albiglutide - placebo) is equal to zero.

B, baseline; LS, least square; MMRM, mixed model repeated measures; MMTT, mixed meal tolerance test; SE, standard error.

Note: Baseline is defined as the last nonmissing value with an assessment date on or before the first day of study medication.

(C)
P values from MMRM analysis of change from baseline in plasma glucagon AUC when comparing albiglutide to placebo were *P* = 0.3696 at week 28 and *P* = 0.7961 at week 52. *P* value is from a 2-sided t-test to test whether the difference of LS Means (albiglutide - placebo) is equal to zero.

AUC, area under the curve; B, baseline; LS, least square; MMRM, mixed model repeated measures; MMTT, mixed meal tolerance test; SE, standard error.

Note: Baseline is defined as the last nonmissing value with an assessment date on or before the first day of study medication.

Figure 3. HbA1c (%) over the duration of the study (intent-to-treat population).

P values from MMRM analysis of change from baseline in HbA1c when comparing albiglutide to placebo were *P* = 0.9204 at week 28 and *P* = 0.8198 at week 52. *P* value is from a 2-sided t-test to test whether the difference of LS Means (albiglutide - placebo) is equal to zero.

B, baseline; LS, least square; MMRM, mixed model repeated measures; SE, standard error.

Note: Baseline is defined as the last nonmissing value with an assessment date on or before the first day of study medication.

Figure 4. Mean daily insulin use over the duration of the study (intent-to-treat population).

P values from MMRM analysis of change from baseline in mean daily insulin use when comparing albiglutide to placebo were *P* = 0.3304 at week 28 and *P* = 0.2338 at week 52. *P* value is from a 2-sided t-test to test whether the difference of LS Means (albiglutide – placebo) is equal to zero.

B, baseline; LS, least square; MMRM, mixed model repeated measures; SE, standard error.

Note: Baseline is defined as the last nonmissing value with an assessment date on or before the first day of study medication.

Figure 5. Mean change from baseline in time spent with plasma glucose level ≤3.9, >3.9 to ≤10.0, and >10.0 (72-hour CGM) at week 52 (intent-to-treat population).

Figure 6. Mean body weight over the duration of the study (intent-to-treat population).

P values from MMRM analysis of change from baseline in mean body weight when comparing albiglutide to placebo were *P* = 0.9684 at week 28 and *P* = 0.9349 at week 52. *P* value is from a 2-sided t-test to test whether the difference of LS Means (albiglutide – placebo) is equal to zero.

B, baseline; LS, least square; MMRM, mixed model repeated measures; SE, standard error.

Note: Baseline is defined as the last nonmissing value with an assessment date on or before the first day of study medication.

Principal Investigators

The authors thank the Principal Investigators who enrolled patients on the study. Below is the list of those who agreed to be acknowledged.

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Table 1. Titration Algorithm for Basal Insulin

Before Breakfast Plasma Glucose[a]		Adjustment of Basal Insulin
mmol/L	mg/dL	U
<3.1[b]	<56[b]	−4
3.1–4.0	56–72	−2
>4.0–5.5	>72–99	No adjustment
>5.5–7.8	>99–140	+2
>7.8	>140	+4

[a]Mean of 2 or more consecutive days of patient's self-monitored plasma glucose values measured before breakfast in the previous 7 days.

[b]Investigator may defer adjustment if there is an obvious reason for the low value, such as a missed meal, or may interrupt or temporarily discontinue insulin if appropriate.

Table 2. Titration Algorithm for Meal-Time Insulin

Plasma Glucose 4 or More Hours After the Preceding Meal[a,b]		Adjustment of Meal-Time Insulin
mmol/L	mg/dL	U[b]
<3.9 without obvious explanation	<70 without obvious explanation	−1, −2[c]
3.9–5.5	70–99	No adjustment
5.6–7.7	100–139	+1
7.8–9.9	140–179	+2
≥10.0	≥180	+3

[a]If basal dose is not optimal, following this algorithm may lead to overdosing.

[b]Mean of 2 or more consecutive days' measurements over the previous 7 days.

[c]At the investigator's discretion, a meal-time insulin dose may be suspended.

Table 3. Demographic and Baseline Clinical Characteristics (Intent-to-Treat Population)

	DEFEND-1	Current Study	
	Placebo (N = 53)	Placebo (N = 15)	Albiglutide (N = 46)
Age, years, mean (SD)	22.7 (4.00)	23.0 (3.96)	22.3 (3.50)
Female sex, n (%)	20 (37.7)	6 (40.0)	21 (45.7)
White race, n (%)	49 (92.5)	15 (100)	46 (100)
Weight, kg, mean (SD)	72.05 (10.80)	69.15 (13.62)	66.04 (11.87)
BMI, kg/m^2, mean (SD)	23.52 (2.63)	22.62 (4.35)	22.26 (3.15)
HbA_{1c}, %, mean (SD)	7.18 (1.61)	7.27 (0.65)	7.30 (1.09)
C-peptide AUC, nmol/L, mean (SD)	0.68 (0.30)	0.59 (0.26)	0.55 (0.30)
Maximum stimulated C-peptide AUC, nmol/L, mean (SD)	0.97 (0.46)	0.86 (0.38)	0.82 (0.45)
Time from diagnosis to first dose of study drug, days, mean (SD)	72.6 (19.72)	51.0 (4.04)	52.8 (3.45)

AUC, area under the curve; BMI, body mass index; HBA_{1c}, glycosylated hemoglobin A_{1c}; SD, standard deviation.

Table 4. Summary of Primary and Secondary Efficacy Endpoint Analyses at Week 52 (intent-to-treat Population)

	Observed Mean Change From Baseline (SD) or Observed Proportion		Model-Adjusted Change From Baseline		Model-Based Treatment Difference
	Placebo (N = 15)	Albiglutide (N = 46)	Placebo (N = 15)	Albiglutide (N = 46)	Difference (Albiglutide – Placebo or Albiglutide:Placebo Odds Ratio)
Primary endpoint (Bayesian analysis)	**Mean (SD)**		**Posterior median (SD), 95% Credible Interval**		**Posterior treatment difference (95% credible interval)**
C-peptide AUC (nmoL/L)	−0.16 (0.37) n = 11[1]	−0.13 (0.24) n = 40[2]	−0.25 (0.04) (−0.32 to −0.17)	−0.13 (0.05) (−0.22 to −0.03)	0.12 (0.00 to 0.24) Probability of treatment difference ≥0.2 nmol/L: 0.097
C-peptide AUC (nmol/L) from DEFEND-1 placebo group	−0.27 (0.31) n = 53[3]				
Primary endpoint (non-Bayesian sensitivity analysis)	**Mean (SD)**		**LS Mean (SE), 95% CI**		**Difference of LS Mean (95% CI)**
C-peptide AUC (nmol/L)	−0.16 (0.37) n = 11[1]	−0.13 (0.24) n = 40[2]	−0.16 (0.07) (−0.31 to −0.02)	−0.13 (0.04) (−0.20 to −0.05)	0.04 (−0.13 to 0.20) *P* = 0.6505
Secondary endpoints					
Maximum stimulated C-peptide (nmol/L)	**Mean (SD)**		**LS Mean (SE), 95% CI**		**Difference of LS Mean (95% CI)**
	−0.32 (0.47) n = 11	−0.18 (0.38) n = 41	−0.29 (0.11) (−0.50 to −0.08)	−0.18 (0.06) (−0.29 to −0.06)	0.11 (−0.13 to 0.35) *P* = 0.3571

Plasma glucagon AUC (ng/L)	**Mean (SD)**		**LS Mean (SE), 95% CI**		**Difference of LS Mean (95% CI)**
	−0.31 (16.00) n = 11	4.66 (13.63) n = 40	2.46 (3.64) (−4.86 to 9.77)	3.53 (1.89) (−0.27 to 7.33)	1.08 (−7.25 to 9.40) *P* = 0.7961
Responder analysis	**n/N (%)**				**Odds ratio (95% CI)**
HbA_{1c} responders	5/12 (42%)	20/41 (49%)	--	--	1.30 (0.33 to 5.05) *P* = 0.6530
Partial remission status	7/12 (58%)	29/41 (71%)	--	--	1.94 (0.46 to 8.16) *P* = 0.4127
HbA_{1c} (%)	**Mean (SD)**		**LS Mean (SE), 95% CI**		**Difference of LS Mean (95% CI)**
	−0.73 (1.03) n = 12	−0.59 (1.65) n = 43	−0.74 (0.39) (−1.51 to 0.04)	−0.64 (0.21) (−1.07 to −0.21)	0.10 (−0.78 to 0.99) *P* = 0.8198
Mean daily insulin dose (units/kg/d)	**Mean (SD)**		**LS Mean (SE), 95% CI**		**Difference of LS Mean (95% CI)**
	0.04 (0.12) n = 12	0.11 (0.22) n = 41	0.02 (0.06) (−0.09 to 0.13)	0.10 (0.03) (0.04 to 0.16)	0.08 (−0.05 to 0.20) *P* = 0.2338
72-h CGM: time (h/d) spent with plasma glucose level	**Mean (SD)**		**LS Mean (SE), 95% CI**		**Difference of LS Mean (95% CI)**
≤3.9 mmol/L	0.96 (1.45) n = 10	0.53 (2.00) n = 31	1.04 (0.61) (−0.19 to 2.27)	0.64 (0.34) (−0.06 to 1.33)	−0.41 (−1.81 to 1.00) *P* = 0.5593
>3.9 to ≤10 mmol/L	−3.11 (5.30) n = 10	−2.06 (4.29) n = 31	−2.60 (1.45) (−5.53 to 0.33)	−2.25 (0.81) (−3.89 to −0.61)	0.35 (−3.00 to 3.69) *P* = 0.8345
>10 mmol/L	2.16 (5.33) n = 10	1.53 (4.35) n = 31	1.86 (1.44) (−1.06 to 4.78)	1.67 (0.81) (0.03 to 3.32)	−0.19 (−3.53 to 3.16) *P* = 0.9114
Body weight (kg)	**Mean (SD)**		**LS Mean (SE), 95% CI**		**Difference of LS Mean (95% CI)**

	0.26 (2.74) n = 12	0.77 (3.50) n = 43	0.82 (0.96) (−1.10 to 2.73)	0.90 (0.52) (−0.14 to 1.95)	0.09 (−2.10 to 2.28) *P* = 0.9349

AUC, area under the curve; CGM, continuous glucose monitoring; HbA_{1c}, glycosylated hemoglobin A_{1c}; SD, standard deviation.[1]Includes patients in the placebo group within the current study with values at baseline and at week 52. Mean (SD) C-peptide AUC at baseline, 0.62 (0.29) mmol/L; week 52, 0.46 (0.40) mmol/L.
[2]Includes patients in the albiglutide group within the current study with values at baseline and at week 52. Mean (SD) C-peptide AUC at baseline, 0.58 (0.30) mmol/L; week 52, 0.45 (0.32) mmol/L.
[3]Includes patients in the DEFEND-1 placebo group. Mean (SD) C-peptide AUC at baseline 0.68 (0.30) mmol/L; week 52, 0.46 (0.31) mmol/L.

Table 5. Summary of Bayesian Sensitivity Analyses of Change From Baseline in Plasma C-Peptide AUC at Week 52

	w = 0[a]	w = 0.5[b]	w = 1[c]
Probability of treatment difference ≥0.2 nmol/L	0.048	0.097	0.095
Probability of treatment difference ≥0.1 nmol/L	0.259	0.638	0.636
Probability of treatment difference ≥0 nmol/L	0.646	0.978	0.978

w, weighting.

[a]Analysis without historical placebo data.

[b]Primary analysis with 50% weight given to historical placebo data.

[c]Analysis with 100% weight given to historical placebo data.

Table 6. Summary of Adverse Events (Safety Population)

	Placebo (N = 17) n (%)	Albiglutide (N = 50) n (%)
Any AE (all treatment phases)	13 (76)	41 (82)
On-therapy AE	13 (76)	41 (82)
On-therapy treatment-related AE	5 (29)	30 (60)
Nausea	3 (18)	19 (38)
Diarrhea	2 (12)	10 (20)
Vomiting	2 (12)	8 (16)
On-therapy AE leading to treatment and/or study withdrawal	2 (12)	0 (0)
On-therapy serious AE	2 (12)	1 (2)
Patient-reported hypoglycemia (on- and posttherapy)		
Any	17 (100)	50 (100)
Severe	0	2 (4)
Documented symptomatic	14 (82)	49 (98)
Asymptomatic	17 (100)	45 (90)
Probable symptomatic	5 (29)	8 (16)

Pseudohypoglycemia	1 (6)	14 (28)
On-therapy AEs of special interest, n (%)		
Hypoglycemic events	17 (100)	50 (100)
Gastrointestinal events	8 (47)	31 (62)
Systemic allergic reactions	1 (6)	0
Injection-site reactions	0	7 (14)
Liver events	0	1 (2)

AE, adverse event.

Table 7. On-Therapy Adverse Events Reported in ≥6% of Patients in Either Treatment Group (Safety Population)

	Placebo (N = 17) n (%)	Albiglutide (N = 50) n (%)
Any adverse event	13 (76)	41 (82)
Nausea	5 (29)	19 (38)
Nasopharyngitis	5 (29)	13 (26)
Diarrhea	2 (12)	13 (26)
Vomiting	4 (24)	10 (20)
Abdominal distension	0	7 (14)
Abdominal pain	0	7 (14)
Decreased appetite	1 (6)	6 (12)
Headache	5 (29)	4 (8)
Abdominal pain, upper	3 (18)	4 (8)
Influenza	0	4 (8)
Anemia	1 (6)	3 (6)
Dyspepsia	0	3 (6)
Gastroenteritis	0	3 (6)
Injection-site erythema	0	3 (6)

Malaise	0	3 (6)
Oropharyngeal pain	0	3 (6)
Asthenia	2 (12)	1 (2)
Folliculitis	2 (12)	0
Lipodystrophy acquired	2 (12)	0

Figure 1

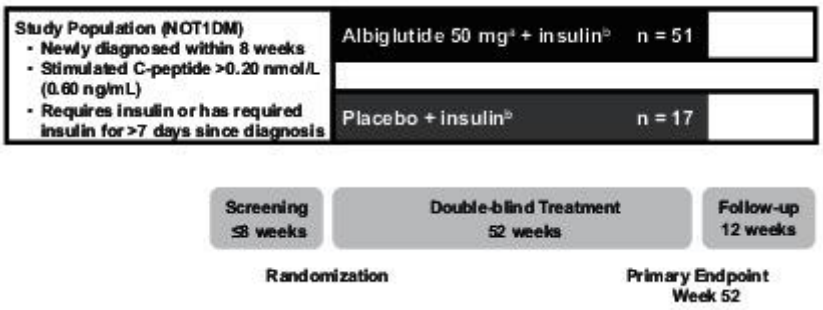
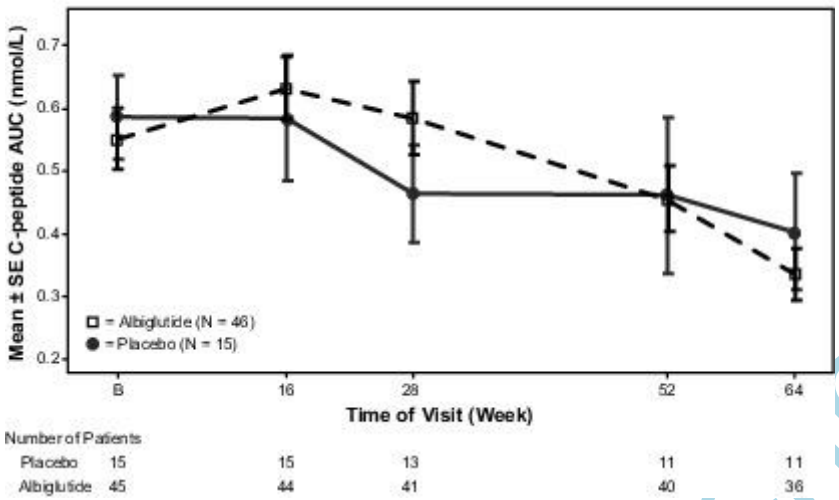


Figure 2A



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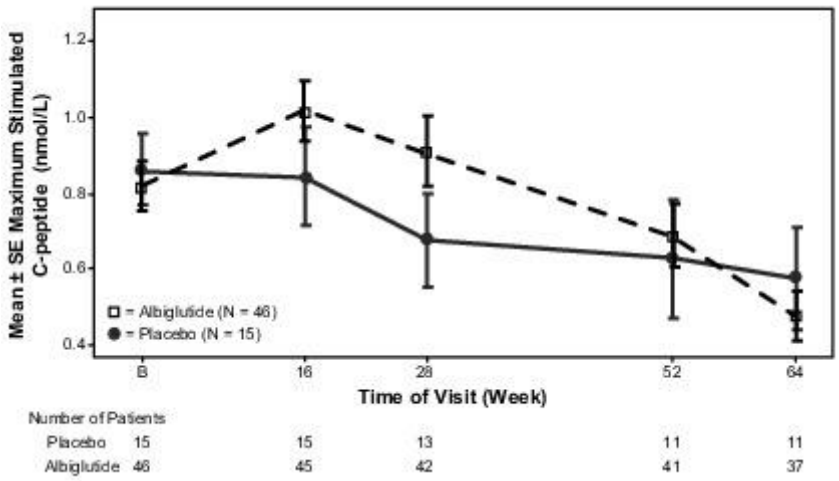

Figure 2C

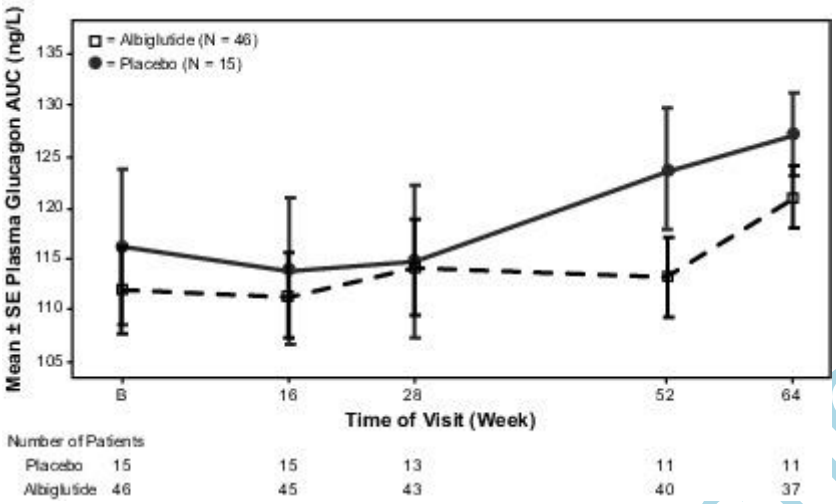

Figure 3

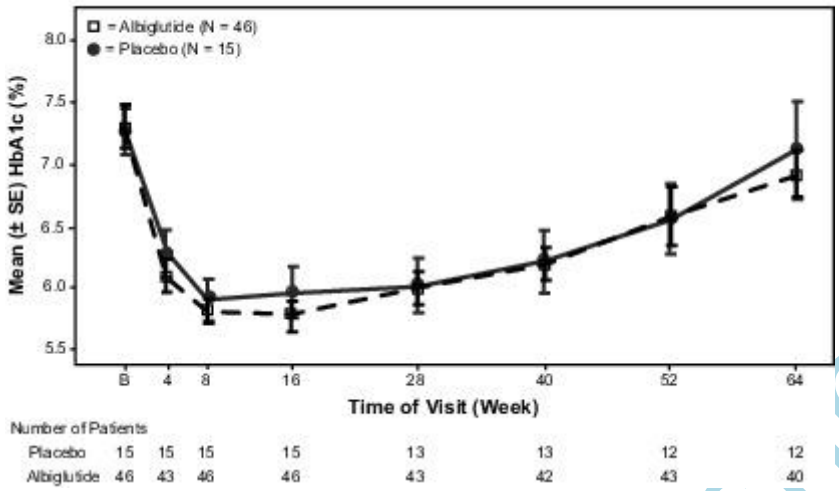

Figure 4A

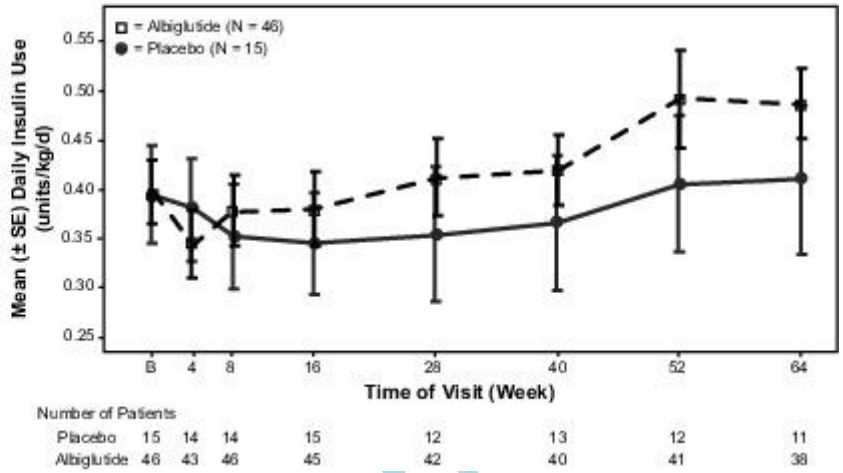

Figure 5

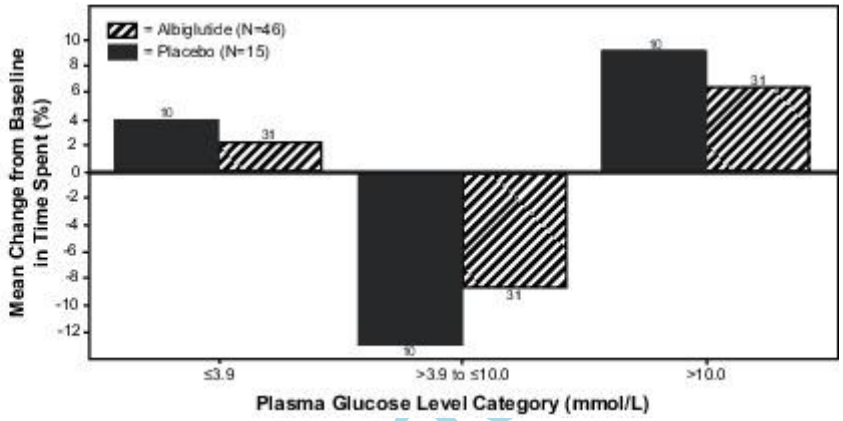

Figure 6A