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MONOGRAPH

ALBIGLUTIDE

Rec INN; USAN

Glucagon-Like Peptide GLP-1 Receptor Agonist
Treatment of Type 2 Diabetes

GSK-716155
Syncria®
Albugon (former brand name)

([8-Glycine]human glucagon-like peptide 1-(7-36)-peptidyl) ([8-glycine]human glucagon-like peptide 1-(7-36)-peptidyl)(recombinant human albumin (585 residues))

CAS: 782500-75-8
EN: 339317

SUMMARY

Glucagon-like peptide 1 (GLP-1) receptor agonists are an important new class of agents for the treatment of type 2 diabetes. Albiglutide is a human GLP-1 receptor agonist developed as a recombinant fusion of two copies of a dipeptidyl peptidase 4 (DPP IV)-resistant human GLP-1 analogue to human albumin. Albiglutide has a long half-life (~5 days) and a narrow peak–trough at steady state, enabling once-weekly dosing. In early clinical studies, albiglutide monotherapy provided improvements in glycemic control, with significant reductions from baseline in glycosylated hemoglobin (–0.80 to –0.90%), fasting plasma glucose (–1.2 to –1.4 mmol/L) and postprandial glucose excursions, and weight loss (–1.1 to –1.7 kg) compared with placebo. The incidence of gastrointestinal adverse events with albiglutide 30 mg weekly was lower than with exenatide and subsided over time, with no further gastrointestinal events beyond 8 weeks of treatment. A comprehensive phase III clinical research program (HARMONY) is investigating the efficacy, safety and long-term durability of albiglutide across a spectrum of disease severity and background characteristics.

BACKGROUND

Although there have been major advances in recent years in the management of type 2 diabetes, the burden of disease remains high. New agents are still needed to treat the underlying pathophysiology and provide durable glycemic control by promoting disease modification. Because of the important role that incretin hormones play in the regulation of glucose homeostasis by directly affecting pancreatic β-cells and α-cells, these molecules have been the focus of much attention in recent years. In healthy individuals, incretin hormones are secreted from the gastrointestinal (GI) tract in response to nutrient intake. They potentiate insulin secretion and inhibit glucagon secretion, both in a glucose-dependent manner, resulting in increased glucose uptake into peripheral tissues and reduced hepatic glucose output (1, 2). However, in patients with type 2 diabetes, the incretin effect is diminished (3).

One of the most important incretin hormones is glucagon-like peptide 1 (GLP-1), a 30-amino-acid peptide (Fig. 1) (2). In patients with type 2 diabetes, some studies have demonstrated that secretion of GLP-1 may be impaired such that GLP-1 levels are low after nutrient intake, which may reflect an underlying defect in type 2 diabetes or may be a consequence of type 2 diabetes and concomitant hyperglycemia and obesity (4). However, the insulinotropic effect of the hormone is retained and infusion of exogenous GLP-1 can restore insulin secretion, suppress abnormally elevated postprandial glucagon secretion and improve glycemic control (1). In addition, short-term infusion of native GLP-1 has been associated with a variety of other effects, including weight loss, delay of gastric emptying and improvement in insulin sensitivity.

In animal models native GLP-1 increases pancreatic β-cell mass, promotes differentiation of islet precursor cells into β-cells, increases the synthesis of proinsulin and reduces the rate of β-cell apoptosis, although to date these effects have not been shown in humans (2). The numerous effects of native GLP-1 have generated significant interest owing to their potential to lead to the development of agents that may improve the treatment of patients with type 2 diabetes. Additionally, if the effects of native GLP-1 on pancreatic β-cells in animal models are also present in humans, agents modulating this pathway offer the disease-modifying potential that may affect the underlying natural course of disease progression, and thus may provide a more durable treatment option. This remains to be demonstrated in long-term, properly controlled clinical trials. The glucose-dependent nature of the actions of GLP-1 offers the potential advantage of improving glycemic control without increasing the risk for hypoglycemia with long-acting GLP-1 receptor agonists.

As the half-life of native GLP-1 is very short (1-2 min), continuous infusion of GLP-1 was required in the initial proof-of-concept studies (5). The impracticality of subcutaneous (s.c.) infusion as a treatment

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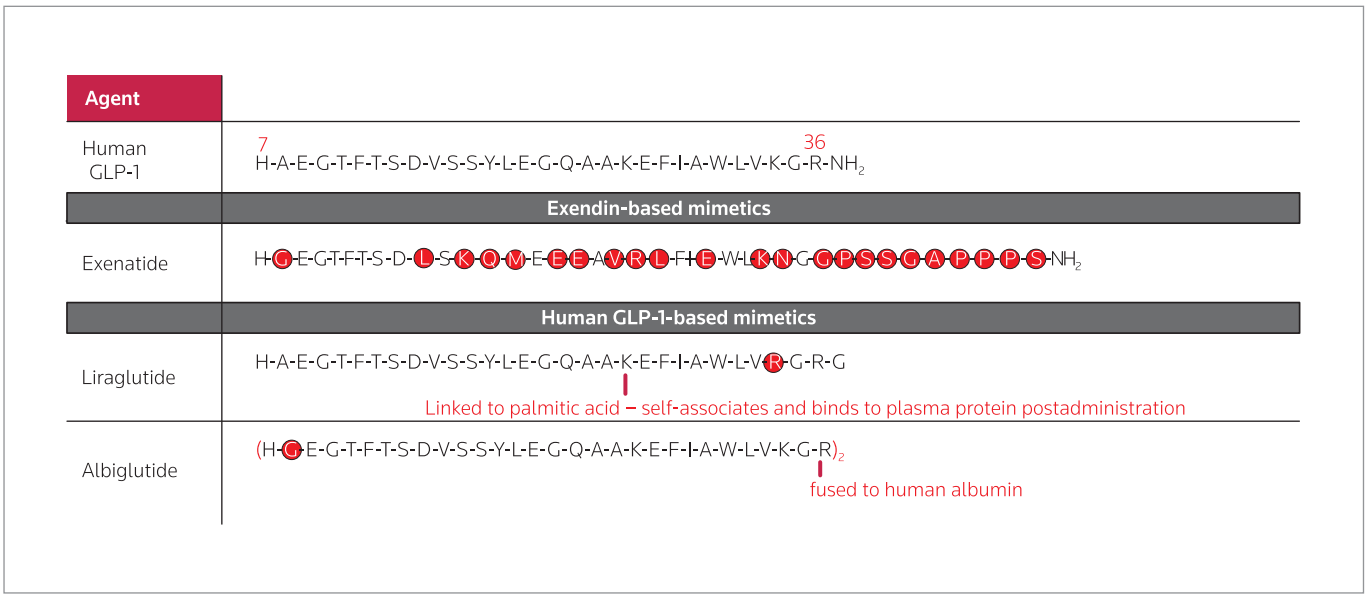

Figure 1. Structure of human glucagon-like peptide 1 (GLP-1), available GLP-1 receptor agonists and albiglutide. Exenatide shares 53% homology with human GLP-1 and liraglutide possesses 97% homology, with a substitution (Lys→Arg) at position 28 and a fatty acid chain attached at position 20 via a glutamoyl spacer. Albiglutide possesses 97% homology to native GLP-1, with a substitution (Ala→Gly) at the dipeptidyl peptidase 4 (DPP IV) cleavage site at position 2. Amino acids in red circles indicate points of non-homology to human GLP-1. Adapted with permission from Drucker and Nauck (2) and Stewart et al. (42).

modality has led to the search for long-acting GLP-1 receptor agonists for the management of type 2 diabetes. The short half-life of GLP-1 is due to rapid deactivation exerted by the protease dipeptidyl peptidase 4 (DPP IV), which cleaves the alanine residue at position 2 of the molecule (1, 2). Two GLP-1 receptor agonists are currently available for the treatment of type 2 diabetes: twice-daily exenatide (synthetic exendin-4, Byetta®; Amylin, Lilly), which shares 53% amino acid homology with human GLP-1, and once-daily liraglutide (Victoza®; Novo Nordisk), which possesses 97% amino acid homology to the native hormone and has an inserted fatty acid side-chain that promotes binding to human albumin post-administration (Fig. 2). The molecular changes in these analogues confer some stability from degradation by DPP IV, with the half-life of exenatide being 2.4 h and that of liraglutide 13 h; however, they still require twice-daily (b.i.d.) and once-daily s.c. administration, respectively (6, 7). A long-acting release formulation (LAR) of exenatide (Bydureon®) is under development to enable once-weekly dosing with this agent and is awaiting Food and Drug Administration (FDA) approval (8).

Both exenatide and liraglutide have been shown to provide improvements in glycemic control, with a reduction in glycosylated hemoglobin (HbA1c) seen in registration trials in the range of 0.5-1.0% and 0.8-1.5%, respectively, with exenatide and liraglutide, associated with indirect measures of improved β-cell function. Body weight loss with these agents has been in the 2- to 3-kg range, and post hoc analyses indicate improvements in cardiovascular risk factors; however, their use is associated with a high frequency of GI adverse events, perhaps slightly less with liraglutide (9-12). There has also been some concern about the formation of antibodies, which have been reported in 40-50% of patients receiving exenatide b.i.d. (13-15), in ~70% of patients receiving the once-weekly formulation (16) and in 4-13% of patients receiving liraglutide (17-19). In general, these antibodies exhibit weak binding affinity, are low titer and do not affect efficacy (9). However, the presence of high-titer antibodies in some patients receiving the once-weekly formulation of exenatide has been associated with neutralizing activity that may potentially impair efficacy (8).

Albiglutide is a GLP-1 receptor agonist macromolecule comprised of two copies of a 30-amino-acid sequence of human GLP-1(7-36) (as a tandem repeat) coupled to recombinant human albumin (rHA). A single substitution (Ala→Gly) at the DPP IV cleavage site of the GLP-1 molecule (20) confers resistance to DPP IV cleavage (21), while retaining a high degree of homology with the native peptide (97%) (Figs. 1 and 2). The plasma half-life of albiglutide is further prolonged to 5 days through binding of the GLP-1 tandem repeat to rHA, a well-studied nonimmunogenic protein carrier that has been used to improve delivery and pharmacokinetic (PK) properties of peptide-based drugs (22). The tandem repeat structure of albiglutide was developed to overcome the reduced potency observed with one GLP-1 moiety bound to rHA. This was believed to be due to impaired interaction of the GLP-1 moiety with its receptor because of the presence of a bulky carrier molecule. Because of its extended half-life compared with native GLP-1 and close homology to the human hormone, albiglutide is being developed as a novel GLP-1 receptor agonist with the potential for weekly or less frequent administration.

PRECLINICAL PHARMACOLOGY

A number of preclinical studies have demonstrated that the mode of action of albiglutide is consistent with that expected of a

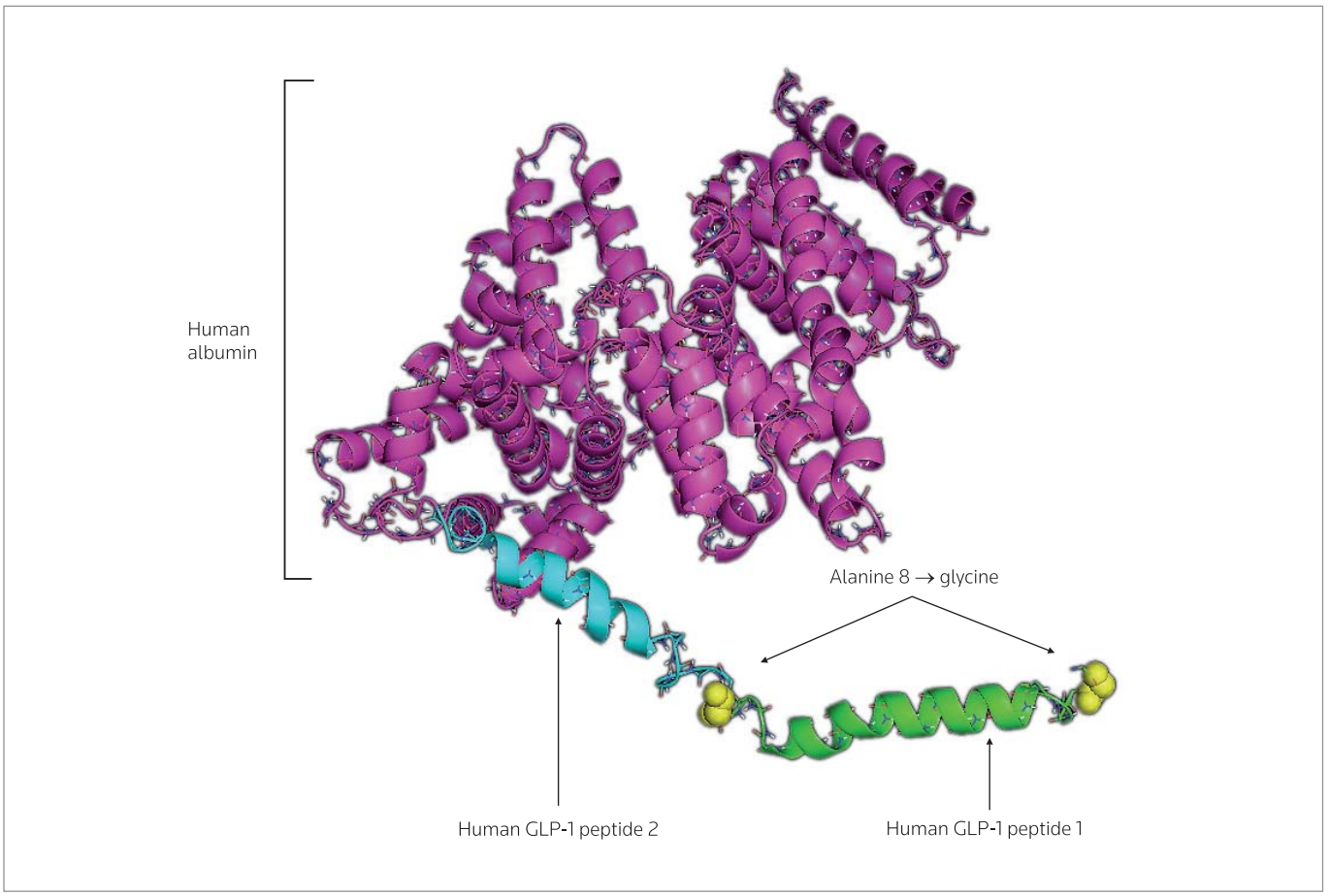

Figure 2. Theoretical structure of albiglutide. Albiglutide is comprised of a tandem repeat of two copies of recombinant human GLP-1(7-36) (blue and green helices) fused to the *N*-terminus of recombinant human albumin (magenta). An alanine → glycine substitution on position 8 of both GLP-1 monomers (yellow spheres) confers resistance to dipeptidyl peptidase 4 (DPP IV).

GLP-1 receptor agonist. For example, in cells expressing human GLP-1, albiglutide induced a concentration-dependent stimulation of cAMP accumulation (23, 24), although at higher concentrations than the native hormone (IC_{50} = 0.606 and 0.019 nM, respectively, for albiglutide and GLP-1) (24). Albiglutide has also been shown to induce in vitro insulin secretion in a concentration-dependent fashion (25). In vivo, albiglutide significantly reduced glycemic excursions and increased insulin levels in wild-type mice, while having no effect on these parameters in GLP-1 receptor knockout mice. In addition, high-dose albiglutide significantly reduced food intake and inhibited gastric emptying in wild-type mice, but not in GLP-1 receptor knockout mice. These observations clearly indicate that albiglutide acts through GLP-1 receptor-dependent mechanisms (23). Resistance of albiglutide to DPP IV degradation has been demonstrated in vitro, with no cleavage of the *N*-terminal sequence observed up to 60 min after incubation with the enzyme. In contrast, 50% cleavage of native GLP-1 fused to rHA was observed after 15 min, and over 80% degradation of the native hormone was observed after 60 min (24).

In *db/db* mice, albiglutide demonstrated dose-dependent reductions in blood glucose, improvement in glucose tolerance and delayed gastric emptying. The effects of albiglutide on food intake and body weight were assessed preclinically in severe combined immunodeficiency (SCID) mice, a strain of nondiabetic immunocompromised mice used to prevent antibody formation to a human antigen. When SCID mice fed a high-fat (60%) diet were administered s.c. albiglutide or rHA, albiglutide significantly reduced weight gain compared with rHA. Additionally, both intracerebroventricular (i.c.v.) and intraperitoneal (i.p.) albiglutide have been shown to reduce food intake, although higher doses of i.p. albiglutide were required to observe an effect (24). Thus, albiglutide appears able to exert anorectic actions following both central and peripheral administration.

In addition, in streptozotocin-treated Wistar rats, albiglutide was associated with dose-dependent increases in β-cell mass, demonstrating protection from streptozotocin-induced β-cell loss (24). In other studies, native GLP-1 and its agonists have been shown to promote proinsulin biosynthesis and the recovery of the first-phase insulin response, reduce β-cell apoptosis, suppress postprandial glucagon and inhibit endogenous glucose production; moreover,

sensitivity of β-cells to incretins may be influenced by the *TCF7L2* variant rs7903146 (2, 25, 26). These effects have not been examined in albiglutide studies to date. Determining whether or not these effects are class effects of GLP-1 agonists may be examined in future research.

PHARMACOKINETICS AND METABOLISM

The PK properties of albiglutide were initially investigated in 39 healthy subjects randomized into 6 cohorts to receive placebo or escalating doses of albiglutide (s.c. to the abdomen) at the following doses on days 1 and 8, respectively: 0.25 and 1 mg, 3 and 6 mg, 16 and 24 mg, 48 and 60 mg, or 80 and 100 mg. Apart from the 0.25-mg dose, which was below quantifiable levels in week 1, the median time to maximum plasma concentration (t_{max}) occurred 2.3-4.0 days postadministration and the mean half-life was in the range of 6-8 days (20).

In a phase IIa repeat-dose study, 54 patients with type 2 diabetes were randomized into 4 cohorts to receive placebo or 9, 16 or 32 mg albiglutide by s.c. injection 30 min before breakfast on days 1 and 8. Patients were not enrolled into the higher dose cohorts until at least 12 subjects had safely completed 2 weeks on the previous lower dose. Median t_{max} occurred 3-5 days postadministration and mean half-life was in the range of 6-7 days for all dose levels. A complementary injection-site study in 46 patients with type 2 diabetes investigating the relative bioavailability and intersubject variability of single doses of 16 or 64 mg albiglutide s.c. to the arm, leg or abdomen demonstrated no significant effects of the injection site on glucose reductions or PK and pharmacodynamic (PD) parameters. A similar t_{max} was recorded across injection sites and doses, with a median of 3-4 days, and mean half-life was in the range of 4-6 days (27).

A 16-week, randomized, placebo-controlled, double-blind, parallel-group phase IIb study compared incremental doses of albiglutide in 3 different dosing schedules (weekly, every other week [biweekly] or monthly) with exenatide b.i.d. as open-label active reference therapy in 356 patients with type 2 diabetes uncontrolled with diet and exercise or metformin (all exenatide patients were treated with metformin, per label). Patients were randomized into 10 treatment arms: placebo matched to albiglutide; exenatide 5 µg b.i.d. for 4 weeks followed by 10 µg b.i.d. for 12 weeks; albiglutide 4, 15 or 30 mg weekly; albiglutide 15, 30 or 50 mg biweekly; and albiglutide 50 or 100 mg monthly. Albiglutide half-life was approximately 5 days and steady-state levels were achieved within approximately 4-5 weeks of the initial dose. The most stable PK profile was observed for the 30-mg weekly dose of albiglutide, with less frequent higher dose regimens leading to greater fluctuations in circulating concentrations of albiglutide (Fig. 3) (28).

The long t_{max} of albiglutide compared with exenatide (approximately 3 days vs. 2.1 h) (6), which indicates gradual absorption, and achievement of a stable plateau may ameliorate the GI intolerance seen with exenatide. In addition, the extended half-life of albiglutide (approximately 5 days) affords the convenience of weekly or even less frequent dosing.

SAFETY

Several studies have assessed the safety and tolerability of albiglutide and demonstrated that this agent exhibits a favorable safety profile over a range of dosing schedules (20, 27). In the 16-week

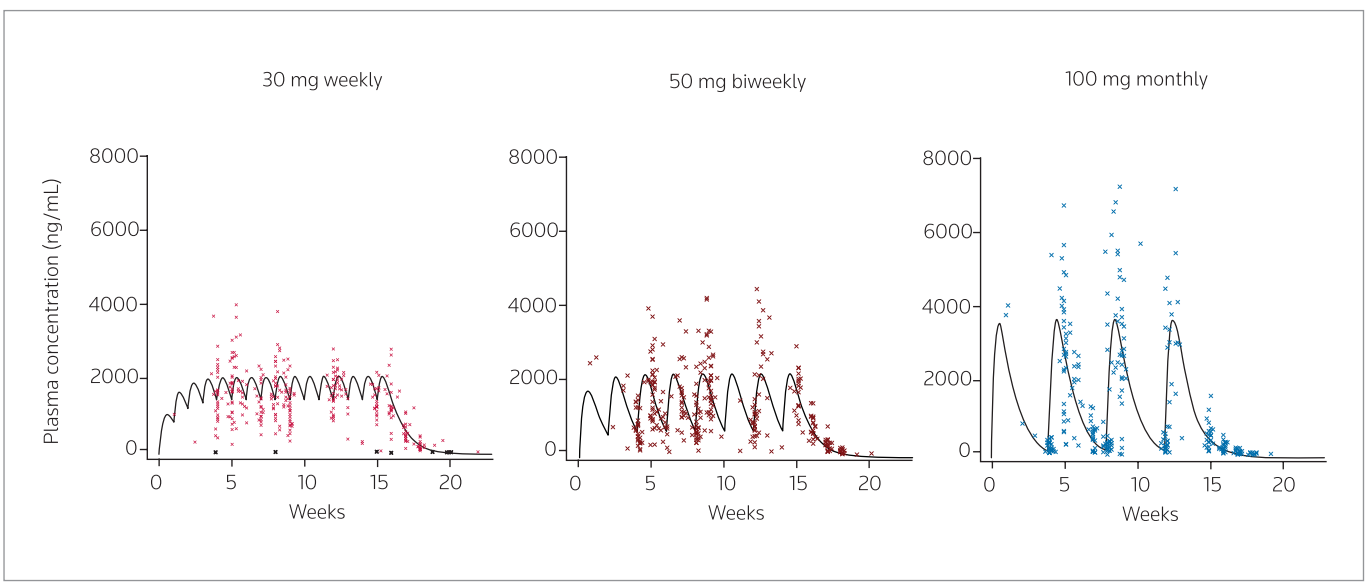

Figure 3. Pharmacokinetic profile of albiglutide. In this 16-week phase IIb study in 356 patients with type 2 diabetes, albiglutide was given subcutaneously in three dosing groups: 4, 15 or 30 mg weekly; 15, 30 or 50 mg every 2 weeks (biweekly); and 50 or 100 mg monthly. Plasma concentrations at the highest dosing level in each group are shown. Plasma levels = scatter plot; population median pharmacokinetic profile = solid line. Adapted from Rosenstock, J., Reusch, J., Bush, M., Yang, F., Stewart, M. *The potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: A randomized controlled trial exploring weekly, biweekly, and monthly dosing.* Diabetes Care, Vol. 33, 2010; 1880-1886. Reprinted with permission from the American Diabetes Association.

phase IIb study described above, the most frequently reported adverse event was nausea, occurring in 12% of patients in the placebo group, 40% of patients receiving exenatide and 14-54% of patients in the albiglutide groups, with the greater frequency seen mainly with higher and less frequent dosing. Of the groups receiving active treatment, the most favorable tolerability profile was observed in the albiglutide 30 mg weekly cohort. A lower proportion of patients in the albiglutide 30 mg weekly group experienced nausea and/or vomiting (29%), compared with the exenatide group (46%). Similarly, within the albiglutide cohorts, a lower proportion of patients in the albiglutide 30 mg group experienced nausea and/or vomiting compared with subjects receiving higher doses (29, 54 and 56%, respectively, for 30 mg weekly, 50 mg biweekly and 100 mg monthly) (28).

When reports of nausea and/or vomiting were analyzed on a weekly basis, a distinct difference in the GI tolerability profiles could be seen among the albiglutide treatment groups (Fig. 4). Of note, 30 mg weekly was associated with < 10% nausea and/or vomiting reported on a weekly basis for the first 8 weeks, and no symptoms were reported thereafter. Weekly reports of nausea and/or vomiting were

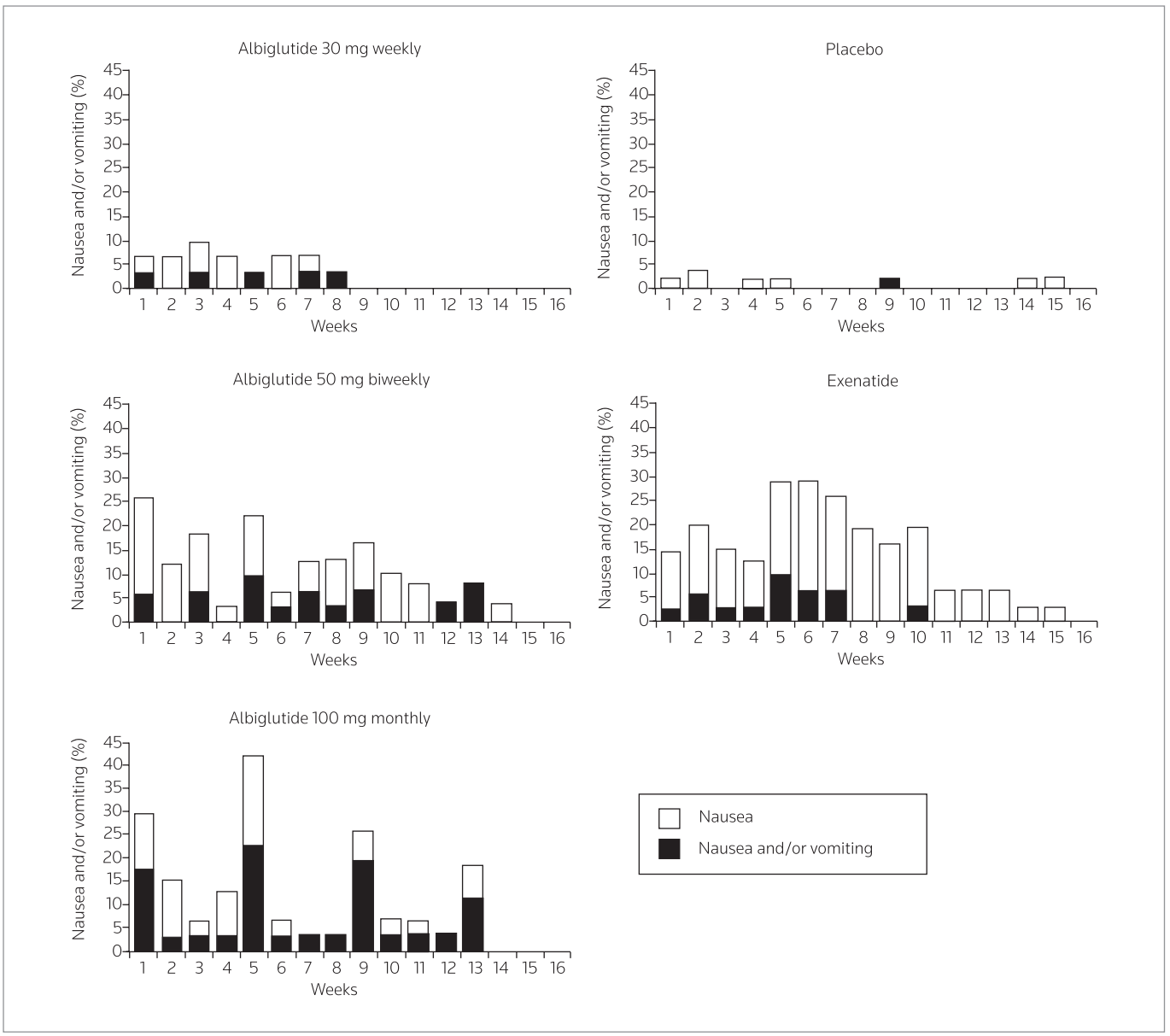

Figure 4. Gastrointestinal adverse events with albiglutide. In the 16-week phase IIb study the most favorable adverse event profile was seen in the albiglutide 30 mg weekly group in which no symptoms of nausea and/or vomiting were reported after 8 weeks. Events of nausea and/or vomiting are shown for the highest doses of albiglutide in the three study groups, exenatide and placebo. Adapted from Rosenstock, J., Reusch, J., Bush, M., Yang, F., Stewart, M. *The potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: A randomized controlled trial exploring weekly, biweekly, and monthly dosing.* Diabetes Care, Vol. 33, 2010; 1880-1886. Reprinted with permission from the American Diabetes Association.

greater for 50 mg biweekly than for 30 mg weekly, but also declined over the study period. For patients receiving the 100 mg monthly dose, there were peaks in the reported incidence after each monthly albiglutide administration. In patients receiving exenatide, the incidence of nausea and/or vomiting peaked at 29% at week 5 (due to label-based titration) and declined over the remainder of the study period (28). Moreover, nausea and vomiting correlated with albiglutide exposure. Compared with biweekly and monthly dosing, weekly dosing of albiglutide had the lowest population median steady-state peak:trough ratio, and also the lowest incidence of GI events (Fig. 5) (29).

There was no increase in documented hypoglycemia with albiglutide (0-3.1%) compared with placebo (3.9%) or exenatide (2.9%). Anti-albiglutide antibodies were detected in only eight (2.5%) patients; however, two of these patients tested positive at baseline and one was in the placebo group. In the other five patients, the appearance of antibodies was mainly transient, and antibodies raised were non-neutralizing, low titer and generally showed crossreactivity with GLP-1. There was no evidence of an association between albiglutide antibodies and efficacy or safety. Skin reactions, which were small and localized to the injection site, were more common in the albiglutide groups (2.9-28.6%) compared with placebo (5.9%) or exenatide (2.9%), but these were not associated with IgE or neutralizing antibodies. It is conceivable that since any skin reaction, regardless of severity, had to be reported as a serious adverse event as part of a rigorous regulatory protocol, this could have led to some ascertainment bias. Skin reactions were not dose-related and did not worsen on repeat dosing. No systemic allergic reactions to albiglutide were recorded (28). Calcitonin levels were not assessed as part of the albiglutide phase II studies but are being assessed in the phase III HARMONY study.

There was consistent weight loss in the albiglutide groups (–1.1 to –1.7 kg for patients receiving the highest dose in each schedule) compared with the placebo group (–0.7 kg). The weight loss with albiglutide was numerically less than that observed with exenatide (–2.4 kg) and there was no significant difference in weight reduction between the treatment groups (28). It is important to note that, although weight loss seen with exenatide was numerically greater than weight loss following treatment with albiglutide, there were weight differences at baseline and no formal statistical comparisons were conducted. Results of the phase III HARMONY program, which includes a variety of active comparators, will further elucidate the effect of albiglutide on weight relative to other antidiabetic therapies.

The number of withdrawals from the study was similar across the treatment groups. The most common adverse events leading to withdrawal included hyperglycemia (0-11.8%, n = 24; mainly in the placebo and lower-dose albiglutide groups), GI events (0-11.4%, n = 10; across groups) and injection-site events (0-9.7%, n = 11; mainly in the higher dose groups) (28).

In summary, the adverse event profile of albiglutide is consistent with its mode of action as a GLP-1 receptor agonist. The pattern of events observed reflects the dose–response relationship seen between plasma concentrations of GLP-1 and its documented physiological effects, in particular the higher incidence of nausea and vomiting seen at higher concentrations of GLP-1 (30). The favorable GI profile of the dose of 30 mg weekly compared with that of exenatide b.i.d. may be attributable to the gradual rise in t_{max} (around 3 days) and stable plateau of drug level (27) compared with the sharper peak (t_{max} = 2.1 h) (6) associated with b.i.d. exenatide.

CLINICAL STUDIES

Clinical research examining the use of albiglutide in patients with type 2 diabetes to date has demonstrated efficacy in terms of glycemic control across a number of different parameters. A short phase I/II, single-blind, placebo-controlled study of albiglutide was carried out in 40 Japanese patients with type 2 diabetes randomized to receive s.c. treatment with albiglutide (n = 32) or placebo (n = 8) over 4 weeks according to the following doses: albiglutide 15 or 30 mg weekly, 50 mg biweekly or 100 mg monthly. After cessation of treatment at 4 weeks, patients were followed up for an additional 5 weeks and pharmacodynamic data were assessed at days 29 and 43 during the follow-up. At days 29 and 43, all doses of albiglutide significantly improved HbA1c by –0.51% to –0.63% from a mean baseline HbA1c of 7.1-8.3% across groups. All doses except 100 mg monthly also significantly reduced fasting plasma glucose (FPG) from baseline compared with placebo (Fig. 6). The lack of significant FPG effects with the dose of 100 mg in the Japanese study may reflect the greater FPG fluctuations that occurred as albiglutide exposure decreased. Of note, comparable reductions in FPG were observed for the albiglutide doses of 30 mg weekly and 50 mg biweekly at days 29 and 43, indicating that a biweekly dosing schedule of albiglutide may be beneficial in some patients with type 2 diabetes. The weekly and biweekly doses were well tolerated in these patients, with an incidence of nausea and vomiting comparable to placebo (31, 32).

In the previously described phase IIa repeat-dose study, evaluation of 24-h glucose profiles demonstrated a reduction in FPG and postprandial plasma glucose (PPG) levels as early as days 2 and 9 in all albiglutide groups, compared with no change in glucose levels in the placebo group. Improvements in PPG levels were observed for all dose levels of albiglutide (27).

Albiglutide provided dose-dependent HbA1c reductions within each dosing schedule of the 16-week phase IIb study. In patients receiving the highest dose in each treatment schedule, HbA1c reductions were –0.87%, –0.79% and –0.87%, respectively, from baseline HbA1c of 8.0%, 7.9% and 8.1%, respectively, for 30 mg weekly, 50 mg biweekly and 100 mg monthly, compared with exenatide –0.54% and placebo –0.17% from baselines of 7.8% and 8.0%, respectively (Fig. 7). The highest dose in each of the regimens significantly reduced HbA1c compared with placebo: 30 mg weekly –0.62% (95% confidence interval [CI]: –1.03 to –0.22; P = 0.003); 50 mg biweekly –0.57% (95% CI: –0.96 to –0.19; P = 0.003); and 100 mg monthly –0.60% (95% CI: –0.99 to –0.22; P = 0.002). No formal statistical comparisons with exenatide were carried out, as it was prespecified to be used as active reference only. Within each dosing schedule, the greatest proportion of patients achieving target HbA1c (< 7%) was observed on each highest albiglutide dose: 52% with 30 mg weekly, 53% with 50 mg biweekly and 48% with 100 mg monthly, compared with 35% and 20% with exenatide and placebo, respectively (28).

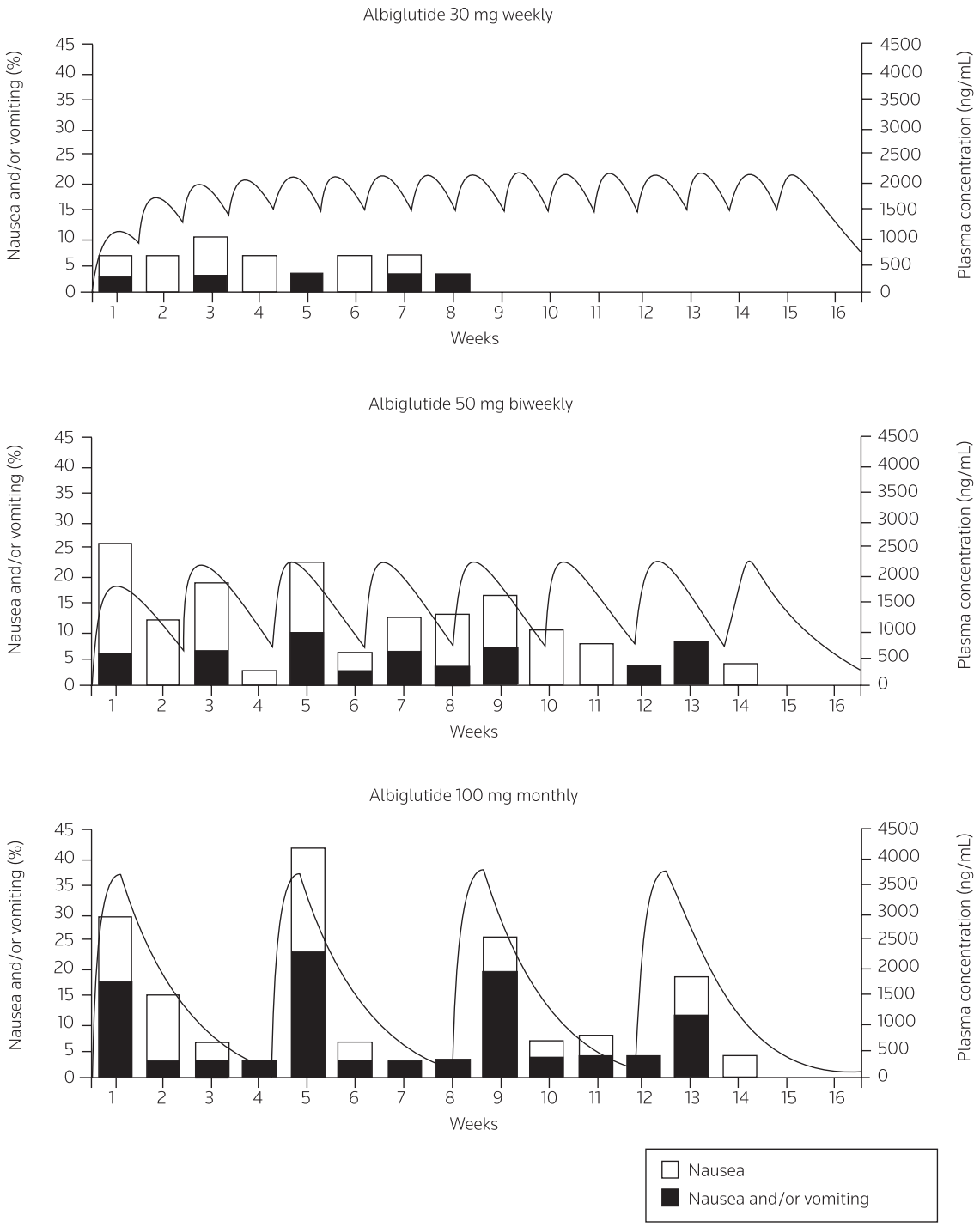

Figure 5. Relationship between predicted albiglutide plasma concentrations and incidence of nausea and vomiting over time. In the 16-week phase IIb study nausea and/or vomiting were correlated with albiglutide exposure and decreased over time. The most favorable gastrointestinal adverse event profile was seen with smaller, more frequent doses of albiglutide (i.e., 30 mg weekly) compared with higher, less frequent doses (50 mg biweekly, 100 mg monthly). Adapted with permission from Stewart, M. et al. (29).

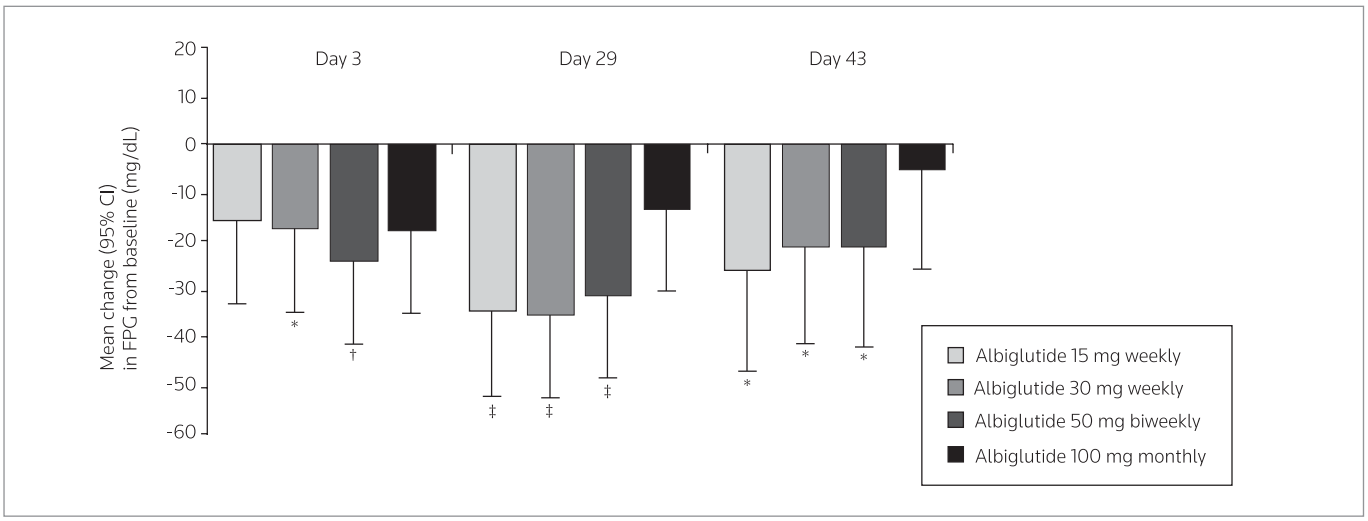

Figure 6. Albiglutide reduces fasting plasma glucose in a Japanese population. This study in 40 patients with type 2 diabetes compared the effect of treatment with albiglutide (15 or 30 mg weekly, 50 mg biweekly or 100 mg monthly) with placebo for 4 weeks. Patients were followed up for 5 weeks. All doses, apart from 100 mg monthly, significantly reduced fasting plasma glucose compared with placebo, and doses of 30 mg weekly and 50 mg biweekly provided comparable reductions on days 29 and 43. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.0001$ vs. placebo. Adapted with permission from Seino et al. (31). Data in the figure are derived from Seino et al. (32).

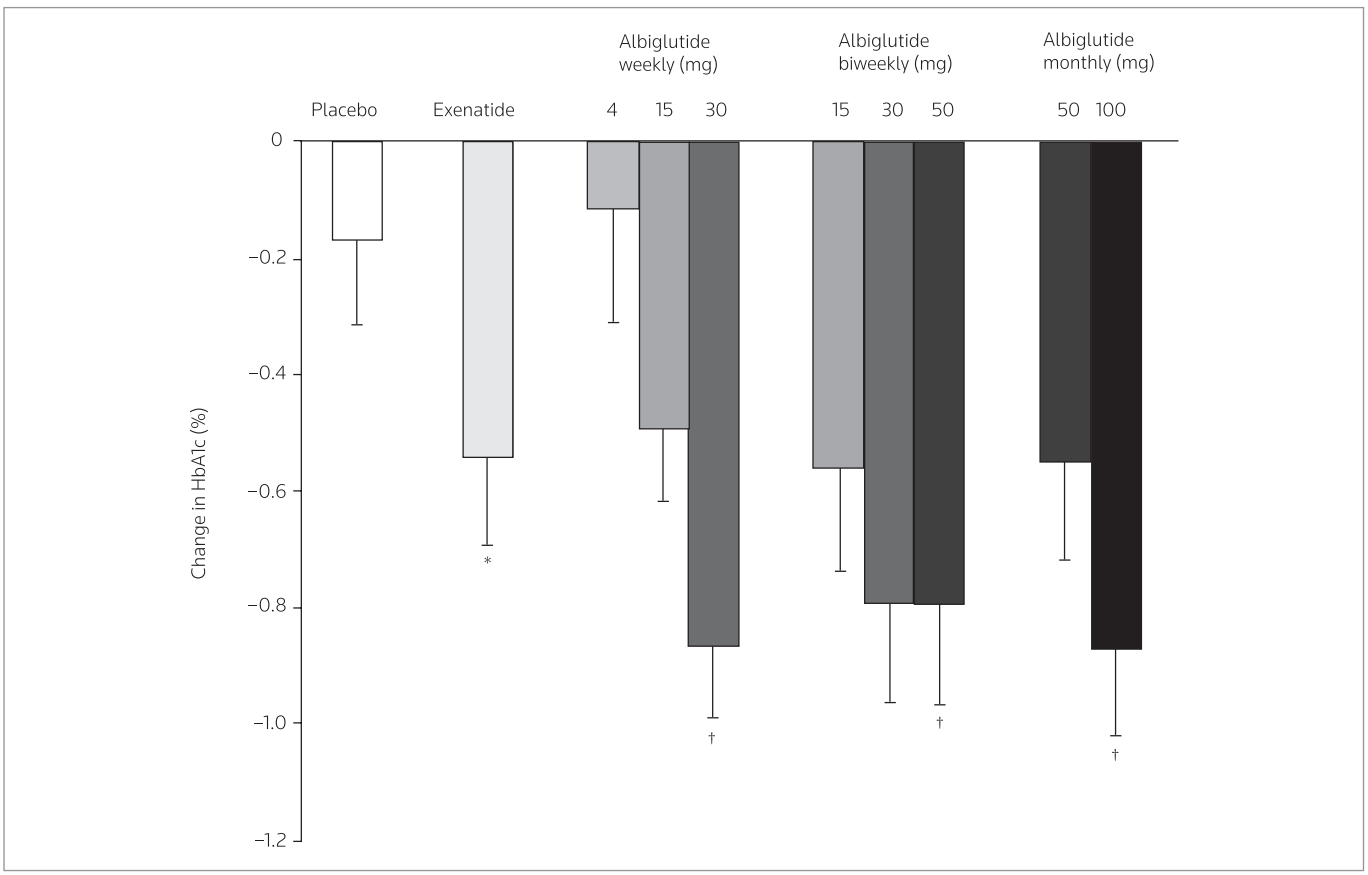

Figure 7. Albiglutide provides dose-dependent reductions in HbA1c. At 16 weeks, the highest albiglutide dose in each of the regimens significantly reduced HbA1c compared with placebo. Data shown are mean ± SE. *No formal statistical comparison versus exenatide (open label). †$P < 0.05$ vs. placebo. Adapted from Rosenstock, J., Reusch, J., Bush, M., Yang, F., Stewart, M. *The potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: A randomized controlled trial exploring weekly, biweekly, and monthly dosing.* Diabetes Care, Vol. 33, 2010; 1880-1886. Reprinted with permission from the American Diabetes Association.

FPG levels declined consistently with albiglutide 30 mg weekly. At the end of 16 weeks, reductions in FPG levels were significantly greater in the 30 mg weekly (–1.4 mmol/L; $P < 0.02$), 50 mg biweekly (–1.2 mmol/L; $P < 0.03$) and 100 mg monthly (–1.2 mmol/L; $P < 0.03$) albiglutide groups compared with placebo, and these reductions were numerically greater than with b.i.d. exenatide; however, no statistical analyses were conducted for this treatment comparison. Although the FPG reductions were comparable for 30 mg weekly, 50 mg biweekly and 100 mg monthly albiglutide after 16 weeks of treatment, there were marked FPG fluctuations over time with the dose of 100 mg monthly, perhaps reflecting the PK profile of this regimen (Fig. 8) (28).

Consistent with the effects of native GLP-1, the phase IIb study revealed improvements in other parameters, including a statistically significant improvement in β-cell function estimated by homeostasis model assessment (HOMA-B) at the doses of 30 mg weekly and 100 mg monthly ($P < 0.05$ vs. placebo after 15 weeks of treatment). The magnitude of change was approximately numerically equivalent to that seen with twice-daily exenatide, although no formal statistical analyses were conducted. Albiglutide was not associated with improvements in insulin sensitivity, as measured by HOMA-IR, and again the magnitude of change was similar to that seen with exenatide. A weight decrease ranging from –0.9 to –1.8 kg over 16 weeks was observed with albiglutide treatment, which was slightly less than that seen with exenatide (Table I). Decreases in both systolic and diastolic blood pressure were also observed, with the group receiving albiglutide 30 mg weekly experiencing a decrease of –5.8 mmHg and –1.9 mmHg, respectively, for systolic and diastolic blood pressure. The magnitude of change was slightly lower than that seen with exenatide. Lipid parameters (total, high-density and low-density lipid cholesterol, and triglycerides) remained stable over the 16 weeks of treatment (28).

In summary, clinical evidence to date on albiglutide shows significant and consistent reductions in HbA1c and FPG across different dosing schemes. HbA1c reductions were similar in weekly, biweekly and monthly treatment groups, but variability in FPG levels and increased GI events were more likely to occur with higher doses of albiglutide administered monthly compared with weekly or biweekly dosing. Albiglutide also demonstrated favorable effects on measures of β-cell function, blood pressure and body weight. The incidence of nausea and/or vomiting reported on a weekly basis was particularly low for patients receiving albiglutide 30 mg weekly (≤ 10% for the first 8 weeks, with no events thereafter) (28).

As a result of the clinical evidence from the dose–response and dose-timing study, albiglutide 30 mg weekly has been selected as the initial dose (with the possibility of uptitration to 50 mg also being assessed) for the phase III HARMONY Clinical Research Program (Table II) (33). The efficacy and safety of albiglutide as

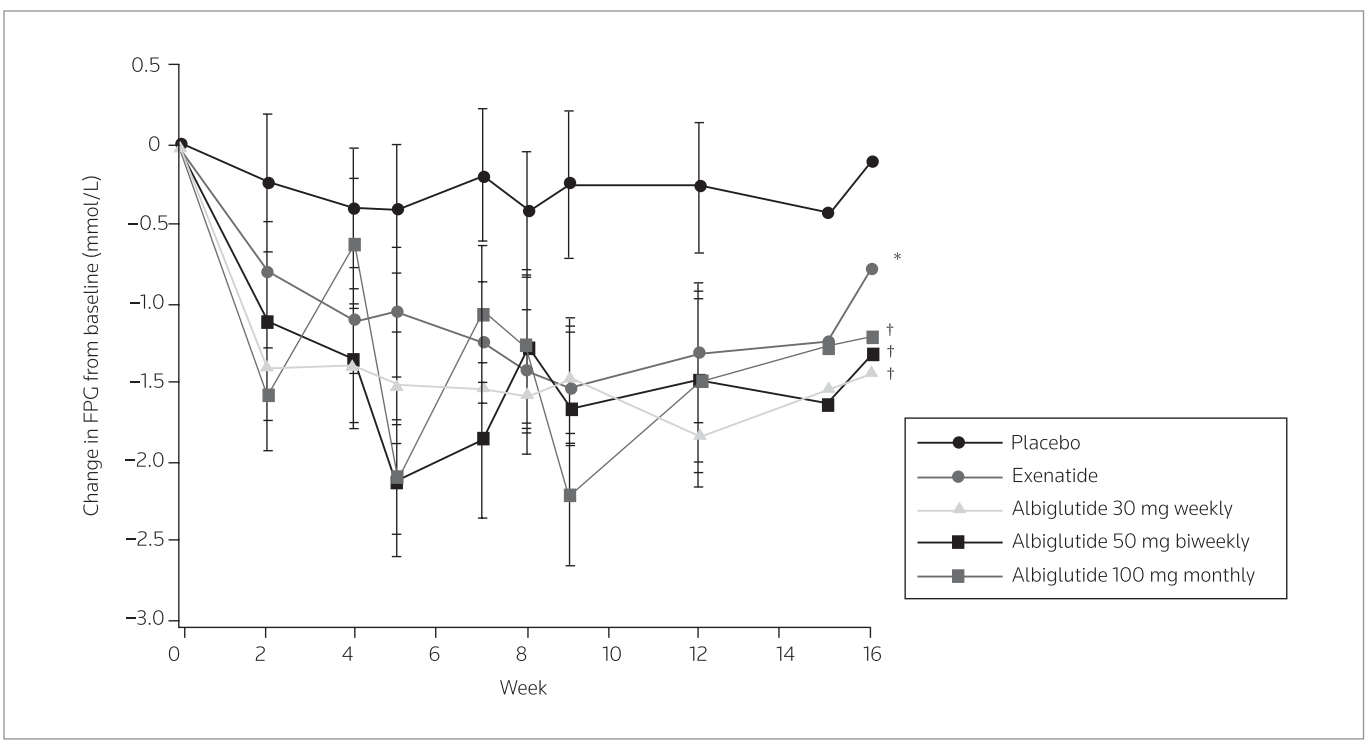

Figure 8. Albiglutide reduces fasting plasma glucose levels (FPG) over time. Time course of FPG for the highest dosing level in the three groups of patients receiving albiglutide, patients receiving exenatide and patients receiving placebo are shown. At 16 weeks, albiglutide provided significantly greater reductions in FPG levels than placebo at the highest dose in the three dosing groups. Data shown are mean ± SE. *No formal statistical comparison versus exenatide (open label). †$P < 0.05$ vs. placebo. Adapted from Rosenstock, J., Reusch, J., Bush, M., Yang, F., Stewart, M. *The potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: A randomized controlled trial exploring weekly, biweekly, and monthly dosing.* Diabetes Care, Vol. 33, 2010; 1880-1886. Reprinted with permission from the American Diabetes Association.

Table I. *Weight loss following treatment with albiglutide in a phase IIb study (27).*

			Albiglutide							
			Weekly			Biweekly			Monthly	
	Placebo	Exenatide	4 mg	15 mg	30 mg	15 mg	30 mg	50 mg	50 mg	100 mg
Weight (kg; mean ± SD	−0.7 ± 2.9	−2.4 ± 3.5	−0.9 ± 1.7	−0.9 ± 2.9	−1.4 ± 2.4	−1.8 ± 2.8	−1.6 ± 2.5	−1.1 ± 2.9	−1.1 ± 3.2	−1.7 ± 3.6

Table II. *The albiglutide HARMONY clinical trial program.*

Study	Background therapy	Comparators	Patients	1º Endpoint
Monotherapy	Diet & exercise (treatment-naïve)	Placebo	315	1 year
Add-on to metformin	Metformin	Sitagliptin, glimepiride or placebo	1,000	2 years
Add-on to pioglitazone	Pioglitazone ± metformin	Placebo	300	1 year
Add-on to metformin + sulfonylurea	Metformin + glimepiride	Pioglitazone or placebo	600	1 year
Head-to-head vs. insulin glargine	Metformin or metformin + sulfonylurea	Insulin glargine	750	1 year
Add-on to insulin glargine	Basal insulin (insulin glargine)	Prandial insulin	500	6 months
Renal impairment	Metformin, pioglitazone, glimepiride or combination	Sitagliptin	600	6 months
Head-to-head vs. liraglutide	Metformin, pioglitazone, glimepiride or combination	Liraglutide	800	36 weeks

monotherapy, as dual therapy in combination with metformin, as triple therapy in combination with metformin/ thiazolidinedione or metformin/sulfonylurea, and as a combination with insulin will be evaluated. Studies will involve active comparisons with a thiazolidinedione, a sulfonylurea, a DPP IV inhibitor, liraglutide and insulin, with flexibility to adequately titrate drugs in order to enable fair comparisons (34-40). In addition, the utility of a biweekly dose will be examined in an appropriate patient population. This program aims to provide physicians with translational insights into how they can introduce albiglutide into treatment paradigms and individualize patient management.

This long-term clinical development program is one of the first full programs to be designed to follow recent FDA guidance on the development of new agents for the treatment of type 2 diabetes (41). The protocols will enable rigorous investigation of cardiovascular safety and, in line with FDA guidance, studies will include patients that are more typical of the population with type 2 diabetes (e.g., patients with a history of cardiovascular and microvascular disease will be included). Examination of cardiovascular risk factors and cardiovascular event adjudication within the HARMONY program may also provide insights into the potential cardiovascular benefits that treatment with a GLP-1 receptor agonist may provide.

Importantly, the HARMONY program will provide the first long-term blinded comparative data on a GLP-1 receptor agonist in a range of combinations in patients representing the spectrum of clinical cases. Studies within the HARMONY program will allow for the assessment of durability of treatment effects following GLP-1 receptor agonist therapy, with measurement of time to treatment failure. This strategy was selected in order to evaluate the hypothesis that GLP-1 receptor agonists may beneficially affect β-cell mass and function, thus delaying the progressive β-cell decline that characterizes type 2 diabetes and reduce the need for frequent treatment escalation in order to meet glycemic targets.

The HARMONY program will also extensively examine the positioning of albiglutide within the treatment algorithm by using a range of active comparators. The addition of albiglutide to metformin will be contrasted with the addition of a DPP IV inhibitor to metformin, providing valuable evidence with respect to the relative clinical merits of the two classes of agents that take advantage of the GLP-1 pathway. In addition, the ability of albiglutide to provide an alternative to basal insulin after oral therapy is no longer effective will also be examined. Compared with the addition of once-daily basal insulin, once-weekly albiglutide will offer a more convenient treatment regimen and may also reduce the incidence of hypoglycemia and weight gain that may occur with basal insulin therapy. Similarly, when comparing the addition of prandial insulin to basal insulin, the addition of once-weekly albiglutide to optimized basal insulin offers the potential for greater convenience with substantially fewer injections, reduced risk of hypoglycemia, more favorable effects on body weight and similar or better glycemic control. Notably, relatively few studies are available comparing the addition of a GLP-1 analogue to basal insulin, and the studies available to date are generally small and uncontrolled. Thus, the HARMONY program will provide new insights into the most optimal strategies for the clinical use of GLP-1 receptor agonists.

CONCLUSIONS

The development of GLP-1 receptor agonists is a promising new approach for the treatment of patients with type 2 diabetes, and new agents in this class offer the potential to improve on the benefits already observed. Albiglutide possesses a unique structure, with close homology to the native GLP-1 hormone and molecular stability afforded by incorporated binding to rHA. These features make it a

promising addition to this class, in particular due to its long half-life, which enables once-weekly or less frequent dosing, and distinct PK characteristics that may result in better GI tolerance, which may lead to further clinical benefits.

Studies to date have shown that albiglutide improves glycemic control with consistent HbA1c reductions across a variety of doses and dosing schedules (i.e., 30 mg weekly, 50 mg biweekly and 100 mg monthly), and that 30 mg weekly provides stable reductions in FPG, while minimizing the GI side effects that are characteristic of the class. In addition, albiglutide has demonstrated a favorable safety/tolerability profile in phase II studies to date, with a low risk of hypoglycemia and a low incidence of anti-albiglutide antibodies. Albiglutide is currently being investigated in a comprehensive phase III clinical development program designed to assess its efficacy, safety and durability in a clinically representative wide patient population with a range of active comparators.

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