



Advancing Basal Insulin Replacement in Type 2 Diabetes Inadequately Controlled With Insulin Glargine Plus Oral Agents: A Comparison of Adding Albiglutide, a Weekly GLP-1 Receptor Agonist, Versus Thrice-Daily Prandial Insulin Lispro

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OBJECTIVE

GLP-1 receptor agonists may provide an alternative to prandial insulin for advancing basal insulin therapy. Harmony 6 was a randomized, open-label, active-controlled trial testing once-weekly albiglutide vs. thrice-daily prandial insulin lispro as an add-on to titrated once-daily insulin glargine.

RESEARCH DESIGN AND METHODS

Patients taking basal insulin (with or without oral agents) with HbA_{1c} 7–10.5% (53–91 mmol/mol) entered a glargine standardization period, followed by randomization to albiglutide, 30 mg weekly ($n = 282$), subsequently uptitrated to 50 mg, if necessary, or thrice-daily prandial lispro ($n = 281$) while continuing metformin and/or pioglitazone. Glargine was titrated to fasting plasma glucose of <5.6 mmol/L, and lispro was adjusted based on glucose monitoring. The primary end point was the difference in the HbA_{1c} change from baseline at week 26.

RESULTS

At week 26, HbA_{1c} decreased from baseline by $-0.82 \pm SE 0.06\%$ (9.0 mmol/mol) with albiglutide and $-0.66 \pm 0.06\%$ (7.2 mmol/mol) with lispro; treatment difference, -0.16% (95% CI -0.32 to 0.00 ; 1.8 mmol/mol; $P < 0.0001$), meeting the noninferiority end point (margin, 0.4%). Weight decreased with albiglutide but increased with lispro (-0.73 ± 0.19 kg vs. $+0.81 \pm 0.19$ kg). The mean glargine dose increased from 47 to 53 IU (albiglutide) and from 44 to 51 IU (lispro). Adverse events for albiglutide versus lispro included severe hypoglycemia (0 vs. 2 events), documented symptomatic hypoglycemia (15.8% vs. 29.9%), nausea (11.2% vs. 1.4%), vomiting (6.7% vs. 1.4%), and injection site reactions (9.5% vs. 5.3%).

CONCLUSIONS

Weekly albiglutide is a simpler therapeutic option than thrice-daily lispro for advancing basal insulin glargine therapy, resulting in comparable HbA_{1c} reduction with weight loss and lower hypoglycemia risk.

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Because β -cell function progressively declines in type 2 diabetes, most people will ultimately require exogenous insulin therapy to meet glycemic goals. A common approach for initiating insulin therapy is the addition of basal insulin to oral agent therapy (1). Clinical trials have demonstrated that basal insulin analogs can effectively treat glycemic targets when structured insulin adjustment algorithms are systematically used (2). However, only 50–60% of patients reach glycemic goals, and the number may be lower in clinical practice if basal insulin replacement is not properly optimized (3–5). When the addition of basal insulin to oral agents is insufficient to achieve adequate glycemic control, injections of prandial insulin are often added (6). The addition of prandial insulin to basal insulin has been shown to further reduce HbA_{1c} levels compared with basal insulin alone (7,8). However, this approach is generally limited by hypoglycemia and weight gain (9,10).

Recent studies have shown that GLP-1 receptor agonists (RAs) used in conjunction with basal insulin have complementary effects resulting in meaningful glucose-lowering benefits. Basal insulin analogs provide diurnal and especially nocturnal coverage of postabsorptive periods, reducing hepatic glucose production and resulting in improvements in nocturnal and fasting plasma glucose (FPG) levels (2). GLP-1 RAs stimulate insulin secretion and suppress glucagon secretion, both in a glucose-dependent manner, with marked reductions in postprandial glucose levels (11–13), thereby providing a complementary mechanism of action to basal insulin. In addition, weight loss often experienced with GLP-1 RAs can counteract weight gain with exogenous insulin therapy. Randomized, placebo-controlled trials evaluating use of GLP-1 RAs in conjunction with basal insulin have demonstrated meaningful reductions in glycated hemoglobin A_{1c} (HbA_{1c}), weight loss, and low risk of hypoglycemia (14–18).

Albiglutide is a GLP-1 RA composed of a GLP-1 dimer fused to recombinant human albumin. An amino acid substitution at position eight of the GLP-1 dimer creates resistance to dipeptidyl peptidase-4 (DPP-4) degradation. Albiglutide has a half-life of ~5 days, allowing for weekly dosing (19–23). In a phase

2b dose-ranging study, once-weekly albiglutide was associated with numerically greater improvement in HbA_{1c} versus twice-daily exenatide and substantially less nausea and vomiting (22).

Adding once-weekly albiglutide to type 2 diabetes insufficiently controlled on insulin glargine may provide glycemic control to a difficult-to-treat population in a more convenient and simpler manner than advancing to the conventional basal/bolus regimen. The present trial evaluated the efficacy and safety of once-weekly albiglutide versus thrice-daily prandial lispro added to titrated basal glargine in patients with type 2 diabetes uncontrolled with glargine with or without oral antihyperglycemic agents. To our knowledge, this is the first trial to directly compare these two intensification approaches in patients with type 2 diabetes taking basal insulin with inadequate glycemic control. The full study was 52 weeks in duration. Results to the primary end point of 26 weeks are reported here.

RESEARCH DESIGN AND METHODS

Patients

This study was conducted in accordance with Good Clinical Practice standards, all applicable privacy requirements, and the guiding principles of the Declaration of Helsinki. Institutional review board approval was received, and written informed consent was obtained from each patient before participation in the study.

Key inclusion criteria were men or women aged 18–75 years; type 2 diabetes inadequately controlled on glargine, detemir, or NPH insulin, with or without oral antidiabetes drugs, for ≥ 6 months and < 5 years; HbA_{1c} $\geq 7.0\%$ (53 mmol/mol) and $\leq 10.5\%$ (91 mmol/mol); and BMI ≥ 20 kg/m² and ≤ 45 kg/m². Major exclusion criteria were ongoing symptomatic biliary disease or history of pancreatitis, lipase level above upper limit of normal (ULN), recent clinically significant cardiovascular or cerebrovascular disease, and history or family history of medullary carcinoma or multiple endocrine neoplasia type 2 (full criteria are in the Supplementary Methods).

Study Design

Harmony 6 was a randomized, open-label, active-controlled, parallel-group, multicenter phase 3 study. The study comprised four periods: screening,

run-in/stabilization to insulin glargine (4–8 weeks), 52-week treatment, with the primary outcome at 26 weeks reported here, and an 8-week follow-up (Supplementary Fig. 1). Patients taking other intermediate- or long-acting insulins were switched to glargine, and their dose was titrated/stabilized over ~8 weeks. Patients continued taking their current regimen of metformin (MET), pioglitazone (PIO), and α -glucosidase inhibitors for the duration of the study. Use of sulfonylureas, glinides, or DPP-4 inhibitors was discontinued at week –1 per protocol.

Patients were stratified by HbA_{1c} ($\leq 8.5\%$ [69 mmol/mol] or $> 8.5\%$ [69 mmol/mol]), history of myocardial infarction (yes or no), and current oral therapy (MET without PIO, PIO without MET, both, or neither). The two treatment arms were 1) albiglutide, 30 mg weekly, uptitrated to 50 mg if necessary, + once-daily titrated glargine; or 2) thrice-daily titrated prandial lispro + once-daily titrated glargine.

Before week 8, albiglutide uptitration was not allowed. If HbA_{1c} was $> 8\%$ between weeks 8 and 12, albiglutide could be uptitrated to 50 mg once weekly. Similarly, if HbA_{1c} was $\geq 7.5\%$ between weeks 12 and 26, uptitration of albiglutide was allowed.

Glargine was titrated similarly to achieve FPG of < 5.6 mmol/L in both groups according to an insulin titration scheme provided to investigators, which they followed at their discretion. Titration was based on FPG measurements from the preceding 2 days (based on self-monitoring of blood glucose), and recommended insulin increases ranged from 2 IU to 8 IU, depending on the degree of hyperglycemia. Insulin dose could also be decreased in the case of hypoglycemia, and was to be decreased by 10–15% in the case of severe hypoglycemia (Supplementary Table 1).

For patients assigned to the lispro arm, prandial insulin was started based on self-monitored blood glucose data and distributed among the patient's meal times at the investigator's discretion. The lispro dose was titrated at the investigator's discretion to achieve a preprandial glucose level of 4.4–7.2 mmol/L and peak (1–2 h) postprandial glucose of < 10 mmol/L based on average of the two previous days' home glucose-monitoring results (before

and 2 h after each meal and at bedtime; Supplementary Methods).

Hyperglycemia rescue criteria were specified in the protocol based on laboratory values and titration history. Before week 4, patients were not allowed to receive additional rescue medication to lower blood glucose levels. After week 4, patients were eligible to receive rescue medication if they were not meeting prespecified HbA_{1c} goals (weeks 4–12: 9.0% and <0.5% change from baseline; weeks 12–16: 8.5%; weeks 16–26: 8.0%) and had not received a recent titration. After notification that a patient in either arm met predefined laboratory criteria for hyperglycemia rescue, the investigator reviewed titration history to determine if full rescue criteria were met. Choice of rescue medication, which could include more intensive insulin titration or the addition of other glucose-lowering medications, was determined by the investigator. Addition of other GLP-1 analogs was prohibited, and use of a DPP-4 inhibitor as rescue was discouraged.

The primary objective was to evaluate the efficacy of albiglutide + glargine vs. thrice-daily lispro + glargine on the HbA_{1c} change from baseline at week 26. Secondary efficacy objectives included the change from baseline over time in HbA_{1c} and FPG, proportion of patients meeting HbA_{1c} treatment goals of <7.0% (53 mmol/mol) and <6.5% (48 mmol/mol), change from baseline in weight, and time to meeting hyperglycemia rescue criteria. Safety events of special interest included pancreatitis, thyroid tumors, systemic allergic reactions, immunogenicity, other adverse events (AEs), and abnormalities in laboratory parameters, vital sign measurements, electrocardiograms, and physical examinations. Hypoglycemia severity was defined according to American Diabetes Association criteria (24). Potential cardiovascular events were adjudicated by a cardiovascular end point masked committee, and a separate pancreatitis masked committee adjudicated potential events of pancreatitis. The remit of the pancreatitis adjudication committee included review of all reported AEs of pancreatitis, review of serious AEs to determine if adjudication for pancreatitis was warranted, and review of amylase and/or lipase measurements (≥ 3 times ULN), whether

or not patients had signs or symptoms suggestive of pancreatitis. Criteria for assessing probability of pancreatitis appear in Supplementary Table 2. The committee also assessed the likelihood that pancreatitis cases were attributable to a study drug.

Anti-albiglutide antibodies were measured by indirect ELISA. Samples that were confirmed positive for anti-albiglutide antibodies were further tested by ELISA for GLP-1, glucagon, and human albumin cross-reactivity, as well as albiglutide-neutralizing activity, using a cell-based reporter gene assay.

Statistical Analysis

With 250 patients planned in each treatment group, assuming 10% loss to follow-up, the study would have 94% power to reject the null hypothesis of inferiority for HbA_{1c} change from baseline, assuming an expected treatment group difference of 0.0% and SD of 1.2%, using a one-sided, two-sample *t* test and a test-wise significance level of 0.025 for a noninferiority margin of 0.4%.

Primary analysis of the HbA_{1c} change from baseline response was analyzed using an ANCOVA model that incorporated treatment group, region, age category, and prior myocardial infarction as covariates, with baseline HbA_{1c} as a continuous covariate. The treatment effect estimate for the albiglutide + glargine group was evaluated with this ANCOVA model as least-squares means contrast relative to the preprandial lispro + glargine group. With significance for the noninferiority test, the superiority test for the combination of albiglutide and glargine relative to combination of glargine and preprandial lispro would use a one-sided superiority test at a significance level of 0.025. A multiple-comparisons adjustment strategy was implemented for the multiple inferential tests among the secondary objectives to preserve the study's nominal criterion significance level of 0.05. Missing values for primary end point analysis were imputed using the last observation carried forward. For patients who met laboratory-based hyperglycemia rescue criteria before week 26 or discontinued from active study participation, the HbA_{1c} at the time of rescue was carried forward for the primary end point analysis. Assessments and subsequent

adjustments of both insulins continued beyond rescue. HbA_{1c}, FPG, and body weight changes were analyzed analogous to the primary end point.

The proportions of patients meeting laboratory-based rescue criteria and subsequently rescued or not, through 26 weeks, are summarized. Time to hyperglycemia rescue up to the 6-month primary end point was evaluated using Kaplan-Meier curves. The proportion of patients achieving meaningful response levels was analyzed by treatment comparisons using nonparametric, covariance-adjusted, extended Mantel-Haenszel tests with logistic regression models as supportive analyses.

RESULTS

Overall, 586 patients were enrolled in this study, and 566 received treatment: 285 with albiglutide and 281 with lispro (Fig. 1). More than 90% of patients in each group completed active treatment through week 26. AEs, loss to follow-up, and withdrawal of consent were the most common reasons for discontinuing albiglutide; withdrawal of consent and loss to follow-up were the most common reasons for discontinuation among the lispro group. Three albiglutide-treated patients did not have both baseline and postbaseline HbA_{1c} values and were excluded from efficacy analyses. Most demographic and baseline characteristics were similar between groups (Table 1). Of note, 30 patients (15 per arm) continued sulfonylurea treatment at study entry and during the study.

There was a reduction in HbA_{1c} from a mean (\pm SD) baseline of $8.5 \pm 0.9\%$ (69 mmol/mol) to $7.7 \pm 1.1\%$ (61 mmol/mol) at week 26 in the albiglutide group and from $8.4 \pm 0.9\%$ (68 mmol/mol) to $7.8 \pm 1.1\%$ (62 mmol/mol) in the lispro group. Model-adjusted change from baseline (\pm SE) was $-0.82 \pm 0.06\%$ (9.0 mmol/mol) for albiglutide and $-0.66 \pm 0.06\%$ (7.2 mmol/mol) for lispro. The treatment difference for albiglutide minus lispro of -0.16% (95% CI -0.32 to 0.00) (1.8 mmol/mol) met the prespecified primary end point of noninferiority (0.4%) to lispro ($P < 0.0001$) and was close to meeting the prespecified primary end point of statistical superiority ($P = 0.0533$). Decreases from baseline over time in HbA_{1c} were observed through week 26 in both groups, with a steep decline

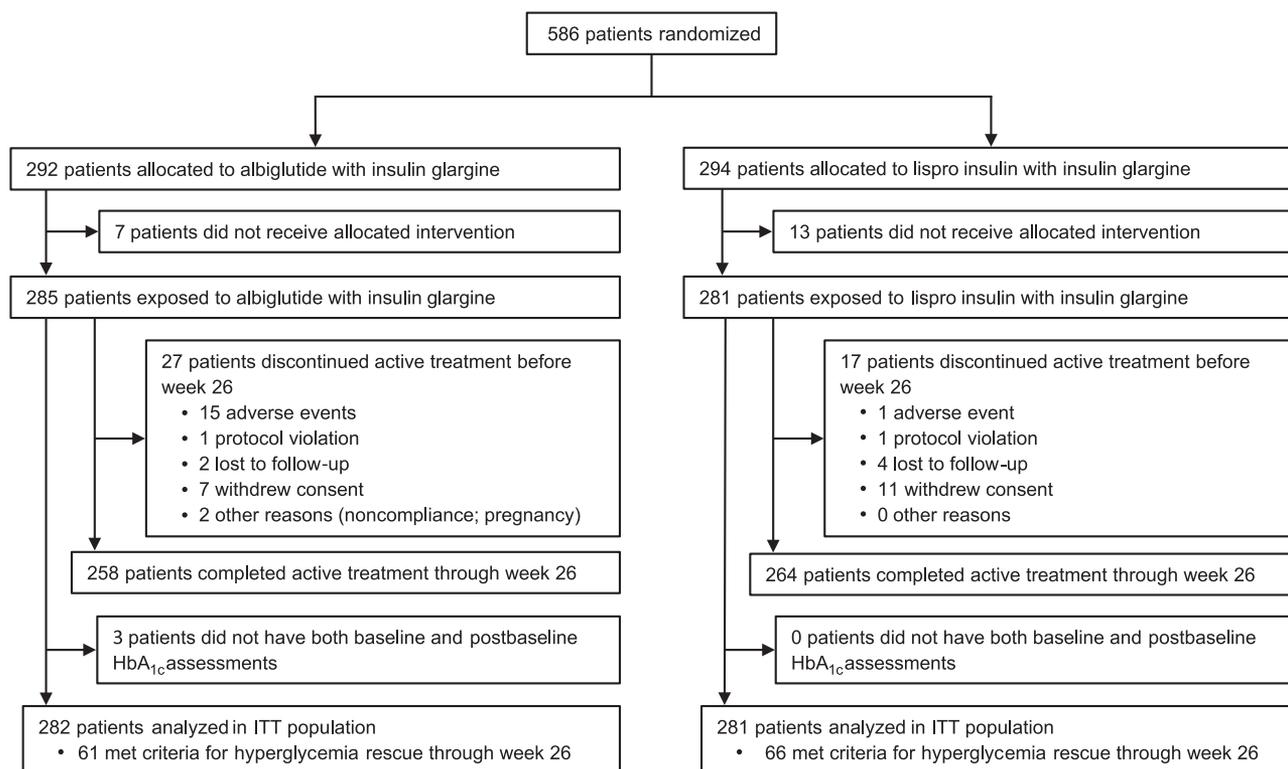


Figure 1—Patient disposition. ITT, intent to treat.

from baseline to week 8 (Fig. 2A). At each visit, the magnitude of change from baseline was numerically greater in the albiglutide group versus the lispro group. A sensitivity analysis that used observed HbA_{1c} values with no missing data imputation showed findings consistent with the intent-to-treat population. An exploratory post hoc analysis was also done to examine change from baseline in HbA_{1c} in patients as a function of whether they continued sulfonylurea therapy. Results from patients who discontinued sulfonylurea were comparable with overall results. Descriptive statistics excluding patients who continued on sulfonylurea appear in Supplementary Table 3.

The HbA_{1c} treatment goal of <7.0% (53 mmol/mol) was reached by 30% of patients receiving albiglutide and 25% of those receiving lispro; HbA_{1c} <6.5% (48 mmol/mol) was reached by 11% of albiglutide-treated and 8% of lispro-treated patients at week 26. Changes in FPG were consistent with HbA_{1c} changes over time, decreasing in both groups at all on-treatment visits (Fig. 2B). Mean FPG values were lower for the albiglutide group than for the lispro group at each visit. The difference did not meet statistical significance at the time of the 26-week primary end point

(−0.99 vs. −0.71 mmol/L; $P = 0.2366$). The glargine dose increased similarly in both the albiglutide (baseline, 47.0 IU; 26 weeks, 53.2 IU) and lispro (baseline, 43.4 IU; 26 weeks, 50.6 IU) arms. The lispro dose increased from 15.5 IU (initial average dose on day of randomization) to 30.6 IU. In the albiglutide arm, 145 patients (51%) uptitrated to 50 mg before week 26.

At 26 weeks, fewer patients in the albiglutide arm (79 [28%]) than in the lispro arm (107 [38%]) met the laboratory-based criteria for rescue, indicating that they were not achieving prespecified glycemic parameters. Among these patients, numerically more patients received rescue therapy in the albiglutide group relative to the insulin lispro group (61 of 79 vs. 62 of 107). Of note, patients meeting laboratory criteria for rescue (indicating that glycemic parameters were not met at a specific time point) may not have actually received rescue therapy in the conventional sense. Rather, they may have recently had more intensive insulin titration or may have received rescue therapy after week 26. Importantly, there was no difference between treatment arms in HbA_{1c} change from baseline at 26 weeks when postrescue values were

included in the analysis (least-squares mean difference, −0.06%; 95% CI −0.22 to 0.11 [0.7 mmol/mol]). Time to hyperglycemia rescue evaluated with a Kaplan-Meier estimate of the probability of hyperglycemia rescue at 6 months was comparable for the two treatment groups (albiglutide, 22.9%; lispro, 24.4%).

Weight decreased from baseline over time in the albiglutide group and increased in the lispro group (Fig. 2C). At week 26, the model-adjusted least-squares mean (SE) weight change from baseline for albiglutide was -0.7 ± 0.2 kg, and the change for lispro was $+0.8 \pm 0.2$ kg ($P < 0.0001$). The between-group difference in weight change from baseline to week 26, -1.5 kg (95% CI -2.1 to -1.0), was significantly different ($P < 0.0001$) in favor of albiglutide at each time point from week 4 through week 26.

Overall, AEs and serious AEs occurred in a similar proportion in the two study arms (Table 2). Gastrointestinal events (most commonly diarrhea, nausea, and vomiting) were relatively low but occurred more frequently in the albiglutide-treated group and were the most common AEs leading to withdrawal (1.4% in the albiglutide arm). However, the incidence of nausea and vomiting

Table 1—Demographics and baseline characteristics

	Insulin glargine in combination with		P value
	Albiglutide (n = 285)	Lispro (n = 281)	
Age, mean ± SD, years	54.8 ± 9.1	56.3 ± 8.9	0.0437
Male, n (%)	132 (46)	136 (48)	NS
Race, n (%)			Not done ^a
Black	39 (14)	34 (12)	
Asian	48 (17)	50 (18)	
White	176 (62)	174 (62)	
Other	31 (11)	24 (9)	
Ethnicity, n (%)			NS
Hispanic/Latino	75 (26)	70 (25)	
Weight, mean ± SD, kg	92.5 ± 21.5	91.6 ± 21.0	NS
Diabetes duration, mean ± SD, years	11 ± 7	11 ± 6	NS
HbA _{1c} , mean ± SD, %	8.5 ± 0.9	8.4 ± 0.9	NS
FPG, mean ± SD, mmol/L	8.5 ± 3.0	8.5 ± 3.1	NS
OAD therapy, n (%) ^b			NS
MET	196 (69)	191 (68)	
TZD	7 (3)	4 (1)	
Both	18 (6)	19 (7)	
Neither	64 (23)	67 (24)	
Prior myocardial infarction	22 (7.7)	27 (9.6)	NS

OAD, oral antidiabetes drug; TZD, thiazolidinedione. ^aThe test for race was not done because patients could check more than one race category; hence, it was not proper to perform test of proportions between two treatment groups. ^bDuring the study, 30 patients (15 per arm) stayed on background sulfonylurea therapy (with or without MET/TZD).

was <5% of patients at all time points in the albiglutide arm, and incidence of vomiting decreased to nearly 0 at 26 weeks (Supplementary Fig. 2). The proportion of patients who had events in the prerescue period was similar to that of the overall population.

Injection site reactions occurred more frequently among those in the albiglutide group versus the lispro group (9.5% vs. 5.3%). All events of injection site reaction were mild or moderate in intensity; 1.1% of patients in the albiglutide group and 0% in the lispro group withdrew from active treatment due to events captured as injection site reactions.

Documented prerescue hypoglycemia occurred nearly twice as frequently in the lispro arm than in the albiglutide arm through week 26 (15.8% of patients and 0.9 events/patient/year vs. 29.9% of patients and 2.3 events/patient/year; Table 2). Severe hypoglycemia occurred in two lispro-treated (0.7%) and in no albiglutide-treated patients. An exploratory post hoc analysis found that rates of hypoglycemia in the small proportion of subjects continuing on sulfonylurea were similar to those in the population overall. Therefore, rates of hypoglycemia in the overall population did not

appear to be driven by patients who remained on sulfonylurea therapy (Supplementary Table 4).

There were six potential systemic allergic reactions in the albiglutide group and three in the lispro group through week 26; none led to withdrawal and most were cutaneous in nature. One patient in the albiglutide arm had a serious AE of angioedema attributed to lisinopril. The patient discontinued lisinopril and remained on the study drug without further events. Anti-albiglutide antibody incidence was 3.3% overall (9 of 269 patients, including 2 with preexisting antibodies); all were nonneutralizing. Among those patients with potential systemic allergic reactions, one patient with an event of injection site erythema tested positive for anti-albiglutide antibodies.

In one albiglutide-treated patient, a thyroid nodule was discovered after a baseline elevated calcitonin level of 140.16 pmol/L (ULN: men, 3.23 pmol/L; women, 1.75 pmol/L), and albiglutide was discontinued after one dose. The patient was subsequently diagnosed with medullary thyroid cancer with confirmed MEN-2b genotype. No events of potential pancreatitis requiring adjudication

occurred during this study. Of note, ~8% of the patients were excluded at the screening visit because of a lipase level greater than the ULN.

CONCLUSIONS

Harmony 6 is the first study to use an active comparator, such as prandial lispro, when a GLP-1 RA was added to basal insulin glargine. Results demonstrated that once-weekly albiglutide plus basal insulin resulted in clinically meaningful HbA_{1c} reduction (−0.82% [9.0 mmol/mol] vs. −0.66% [7.2 mmol/mol] with thrice-daily lispro), which met the prespecified noninferiority margin after 26 weeks. Moreover, albiglutide was associated with weight loss and lower rates of hypoglycemia. As expected, more gastrointestinal AEs occurred with albiglutide than with lispro, although rates of nausea and vomiting were low, at <5% with albiglutide, at all time points. Mild injection site reactions were also more frequent with albiglutide than with lispro, and low rates of anti-albiglutide antibodies were observed.

Trials with both twice-daily exenatide and liraglutide and once-daily lixisenatide in conjunction with basal insulin relative to placebo resulted in glycemic improvements, weight loss, and low risk of hypoglycemia (14–18). The current study adds to this body of knowledge by demonstrating that add-on therapy of once-weekly albiglutide to basal insulin glargine is comparable to adding thrice-daily prandial insulin to basal insulin therapy in improving glucose control with the added value of weight loss, less hypoglycemia, and the obvious simplicity advantage of fewer injections. This finding is especially important in view of the patient-centered approach to hyperglycemia management advocated by the American Diabetes Association/European Association for the Study of Diabetes position statement, and the alternative of using 1 weekly injection versus 21 injections over a 1-week period would be quite appealing to patients (25). In addition to fewer injections, requiring less frequent glucose monitoring may be an additional cost-savings benefit for many people with type 2 diabetes who need to advance basal insulin replacement therapy with a basal/bolus regimen.

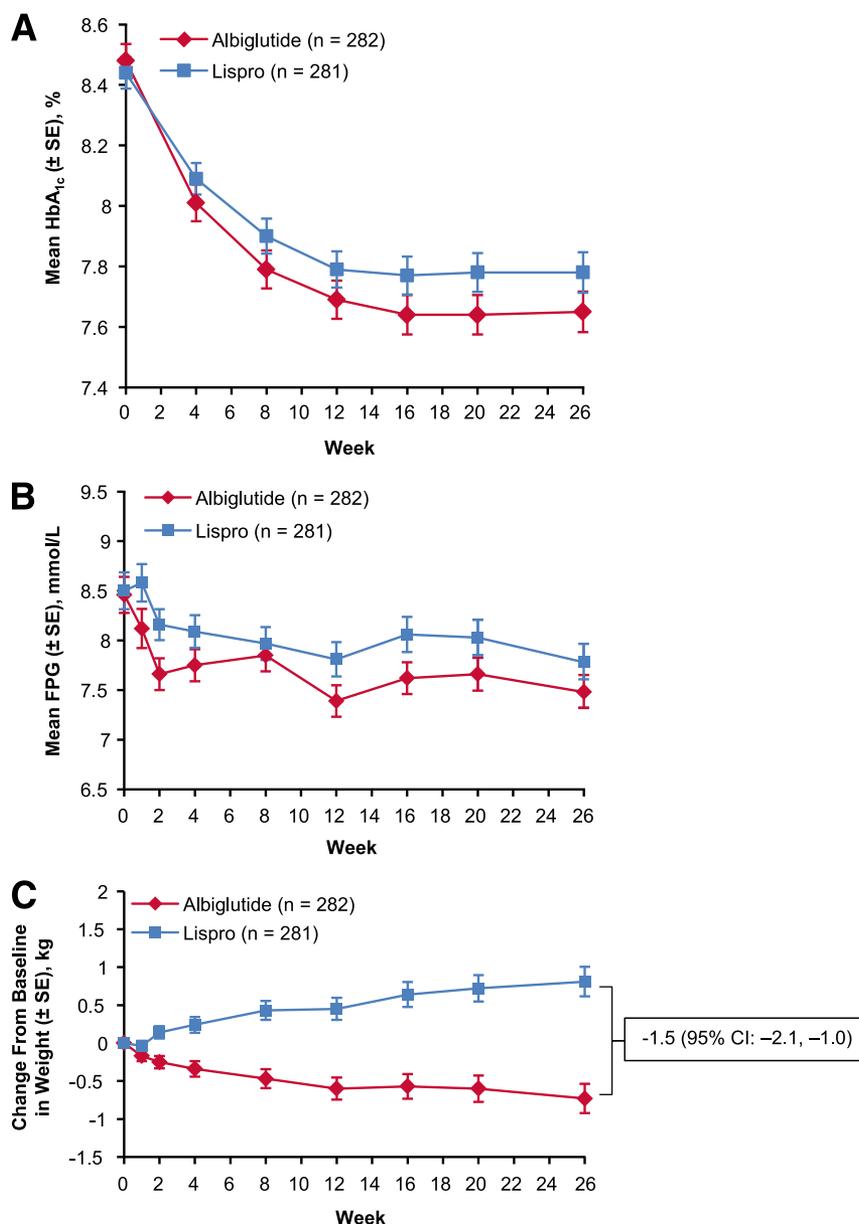


Figure 2—Change over time in mean HbA_{1c} (A), mean FPG (B), and weight (C).

When compared within the GLP-1 RA class, longer-acting agents are associated with less gastric emptying and apparently lower rates of gastrointestinal AEs. Albiglutide has demonstrated lower rates of nausea and vomiting than liraglutide (26) and like weekly exenatide, which was also associated with lower rates versus twice-daily exenatide or versus once-daily liraglutide (27,28). Importantly, rates of nausea and vomiting in the current study were low throughout the course of treatment. This finding may be important for avoiding the early discontinuation of therapy often seen with most GLP-1 RAs,

because nausea and vomiting early in the course of treatment may increase the likelihood of poor adherence, and consequently, poor clinical outcomes. Yearly persistence (defined as medication possession ratio >80%) for twice-daily exenatide and liraglutide has been estimated at only 20% and 31%, respectively (29).

The current study has a number of potential limitations. First, it was not strictly designed as a treat-to-target trial, and no glucose-monitoring committee was involved to enforce the execution of prandial insulin titrations. Second, and for the same reason, titration of basal insulin

glargine was not optimized, as shown by the small increase in insulin glargine dose in both groups after randomization resulting in some further improvements in FPG, but mean values remained above target. Thus, it is conceivable that greater reductions in HbA_{1c} would have been achieved in both arms had the insulin glargine been systematically titrated in a more structured fashion to target FPG <100 mg/dL. This approach would have allowed better appreciation of what further improvements could have been achieved with thrice-daily prandial insulin versus weekly albiglutide as well as the effect on hypoglycemia and body weight

Table 2—AEs occurring in 5% of patients in either arm through week 26 (all events and events occurring prerescue) and hypoglycemia events (prerescue)

Event	≥5% in any treatment group (26 weeks)			
	Albiglutide + insulin glargine (n = 285)		Lispro + insulin glargine (n = 281)	
Overall safety, n (%)				
Any AE	209 (73.3)		199 (70.8)	
Any serious AE	21 (7.4)		19 (6.8)	
Any AE leading to withdrawal	15 (5.3)		1 (0.4)	
Any related event	75 (26.3)		30 (10.7)	
Most common AEs (%)				
Diarrhea	13.0		4.3	
Nausea	11.2		1.4	
Urinary tract infection	8.4		6.0	
Vomiting	6.7		1.4	
Headache	6.7		3.6	
Nasopharyngitis	6.3		7.8	
Upper respiratory tract infection	6.3		3.2	
Diabetic retinopathy	4.9		6.4	
Back pain	3.9		5.0	
Edema peripheral	3.2		5.7	
Hypertension	2.5		5.0	
Most common AEs prerescue period				
Any AE, n (%)	200 (70.2)		183 (65.1)	
Diarrhea (%)	12.6		4.3	
Nausea (%)	10.9		1.4	
Urinary tract infection (%)	8.1		5.7	
Vomiting (%)	6.7		1.4	
Headache (%)	6.3		3.2	
Nasopharyngitis (%)	5.6		7.5	
Upper respiratory tract infection (%)	5.3		3.2	
Diabetic retinopathy (%)	—		—	
Back pain (%)	—		—	
Edema peripheral (%)	—		—	
Hypertension (%)	—		—	
Hypoglycemia events (prerescue) ^a	n (%)	Events (n)/rate ^{b,c}	n (%)	Events (n)/rate ^{b,c}
Any hypoglycemic event ^d	70 (24.6)	188/1.31	107 (38.1)	430/3.09
Severe	0	0	2 (0.7)	2/0.01
Documented symptomatic	45 (15.8)	134/0.94	84 (29.9)	325/2.33
Asymptomatic	19 (6.7)	31/0.22	22 (7.8)	43/0.31
Probable symptomatic	7 (2.5)	8/0.06	8 (2.8)	16/0.11
Relative	11 (3.9)	15/0.10	11 (3.9)	31/0.22
Not applicable	0	0	1 (0.4)	1/0.01
Missing	0	0	2 (0.7)	12/0.09

^aDefinitions according to Workgroup on Hypoglycemia, American Diabetes Association (ADA), 2005. Severity as derived using the ADA guidelines for categorization of hypoglycemic events: severe, requires assistance; documented symptomatic, symptoms, glucose of ≤ 3.9 mmol/L; asymptomatic, no symptoms, glucose ≤ 3.9 mmol/L; probable symptomatic, symptoms, glucose not measured; relative, symptoms, glucose > 3.9 mmol/L. ^bEvent rate per patient-year. ^cRates obtained post hoc. ^dPatients with more than one hypoglycemic event were counted in all severity categories reported.

when used closer to glycemic targets. A further treat-to-target study would be required to understand whether the non-inferiority finding in glucose control would remain under these stricter trial conditions.

Trials in which insulin is more aggressively titrated can achieve lower HbA_{1c} at study end, typically $\sim 7\%$ (3,8,30). However, in studies where less rigorous titration of insulin is done, such as the

A₁chieve trial, the GINGER (Glulisine in Combination with Insulin Glargine in an Intensified Insulin Regimen) trial, and the AT-LANTUS (A Trial Comparing Lantus Algorithms to Achieve Normal Blood Glucose Targets in Subjects With Uncontrolled Blood Sugar With Type 2 Diabetes Mellitus) trial, HbA_{1c} values at study end are consistent with what was seen in the current study ($\sim 7.5\%$) (7,31–33). Greater reductions in HbA_{1c}

would likely have been achieved if the basal glargine dose had been systematically titrated, as shown previously in the twice-daily exenatide added-on to insulin glargine study (14). Although glargine may not have been optimally titrated in this study, the albiglutide-treated patients showed a numerically greater decrease in FPG than did the lispro-treated patients, despite a similar increase in glargine in both groups. This finding is consistent with the fact that long-acting GLP-1R agonists have been shown to have a greater impact on fasting than on postprandial glucose levels.

One additional study limitation is that use of insulin necessitated an open-label approach, which may have biased the reporting of events but was unavoidable given the nature of the compounds tested.

In conclusion, once-weekly albiglutide added-on to basal insulin glargine in type 2 diabetes insufficiently treated with basal insulin and oral antidiabetes drugs resulted in comparable glycemic control but with weight loss, lower risk of hypoglycemia, and fewer injections per week versus thrice-daily lispro and with a relatively low frequency of gastrointestinal AEs for the GLP-1 RA class. This result suggests that once-weekly albiglutide may represent a reasonable option and a simpler approach to therapy intensification in basal insulin-treated patients, where health care support and/or patient willingness to perform the necessary self-management tasks for basal-bolus insulin therapy are limited.

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References

1. Unger J. Insulin initiation and intensification in patients with T2DM for the primary care physician. *Diabetes Metab Syndr Obes* 2011;4:253–261
2. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Scherthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008;51:408–416
3. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. *Diabetes Care* 2008;31:20–25
4. Heintjes EM, Thomsen TL, Penning-van Beest FJ, Christensen TE, Herings RM. Glycemic control and long-acting insulin analog utilization in patients with type 2 diabetes. *Adv Ther* 2010;27:211–222
5. Hermansen K, Davies M, Dereziński T, Martínez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care* 2006;29:1269–1274
6. Ampudia-Blasco FJ, Rossetti P, Ascaso JF. Basal plus basal-bolus approach in type 2 diabetes. *Diabetes Technol Ther* 2011;13(Suppl. 1):S75–S83
7. Davies M, Sinnassamy P, Storms F, Gomis R; AT.LANTUS Study Group. Insulin glargine-based therapy improves glycemic control in patients with type 2 diabetes sub-optimally controlled on premixed insulin therapies. *Diabetes Res Clin Pract* 2008;79:368–375
8. Holman RR, Farmer AJ, Davies MJ, et al.; 4-T Study Group. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009;361:1736–1747
9. Cryer PE. Hypoglycemia: still the limiting factor in the glycemic management of diabetes. *Endocr Pract* 2008;14:750–756
10. Gross JL, Kramer CK, Leitão CB, et al.; Diabetes and Endocrinology Meta-analysis Group (DEMA). Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. *Ann Intern Med* 2011;154:672–679
11. Drucker DJ. The biology of incretin hormones. *Cell Metab* 2006;3:153–165
12. Wajsborg E, Amarah A. Liraglutide in the management of type 2 diabetes. *Drug Des Devel Ther* 2010;4:279–290
13. Wajsborg E, Tavarua A. Exenatide: clinical aspects of the first incretin-mimetic for the treatment of type 2 diabetes mellitus. *Expert Opin Pharmacother* 2009;10:135–142
14. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 2011;154:103–112
15. Lind M, Jendle J, Torffvit O, Lager I. Glucagon-like peptide 1 (GLP-1) analogue combined with insulin reduces HbA1c and weight with low risk of hypoglycemia and high treatment satisfaction. *Prim Care Diabetes* 2012;6:41–46
16. DeVries JH, Bain SC, Rodbard HW, et al.; Liraglutide-Detemir Study Group. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. *Diabetes Care* 2012;35:1446–1454
17. Riddle MC, Forst T, Aronson R, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). *Diabetes Care* 2013;36:2497–2503
18. Rosenstock J, Rodbard HW, Bain SC, et al.; Liraglutide-Detemir Study Group. One-year sustained glycemic control and weight reduction in type 2 diabetes after addition of liraglutide to metformin followed by insulin detemir according to HbA1c target. *J Diabetes Complications* 2013;27:492–500
19. Madsbad S, Kielgast U, Asmar M, Deacon C, Torekov SS, Holst JJ. An overview of once-weekly GLP-1 receptor agonists - available efficacy and safety data and perspectives for the future. *Diabetes Obes Metab* 2011;13:394–407
20. Rosenstock J, Stewart MW. Albiglutide. *Drugs Future* 2010;35:701
21. Bush MA, Matthews JE, De Boever EH, et al. Safety, tolerability, pharmacodynamics and pharmacokinetics of albiglutide, a long-acting glucagon-like peptide-1 mimetic, in healthy subjects. *Diabetes Obes Metab* 2009;11:498–505
22. Rosenstock J, Reusch J, Bush M, Yang F, Stewart M; Albiglutide Study Group. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. *Diabetes Care* 2009;32:1880–1886
23. Tomkin GH. Albiglutide, an albumin-based fusion of glucagon-like peptide 1 for the potential treatment of type 2 diabetes. *Curr Opin Mol Ther* 2009;11:579–588
24. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005;28:1245–1249
25. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012;55:1577–1596
26. Pratley RE, Nauck MA, Barnett AH, et al. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol* 2014;2:289–297
27. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6):

a randomised, open-label study. *Lancet* 2013;381:117–124

28. Buse JB, Drucker DJ, Taylor KL, et al.; DURATION-1 Study Group. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care* 2010;33:1255–1261

29. Chou E, Wang H, Miao W, Germe M, Fournier M, Schwartz S. Adherence to GLP-1 agonist therapy in U.S. managed care. *Diabetes* 2012;61 (Suppl. 1):A314

30. Raskin P, Gylvin T, Weng W, Chaykin L. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes Metab Res Rev* 2009;25:542–548

31. Home P, Naggar NE, Khamseh M, et al. An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: the A1chieve study. *Diabetes Res Clin Pract* 2011;94:352–363

32. Fritsche A, Larbig M, Owens D, Häring HU; GINGER study group. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes—results of the GINGER study. *Diabetes Obes Metab* 2010;12:115–123

33. Oguz A, Benroubi M, Brismar K, et al. Clinical outcomes after 24 months of insulin therapy in patients with type 2 diabetes in five countries: results from the TREAT study. *Curr Med Res Opin* 2013;29:911–920