HARMONY 3: 104-Week Randomized, Double-Blind, Placebo- and Active-Controlled Trial Assessing the Efficacy and Safety of Albiglutide Compared With Placebo, Sitagliptin, and Glimepiride in Patients With Type 2 Diabetes Taking Metformin

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OBJECTIVE
To compare the efficacy and safety of weekly albiglutide with daily sitagliptin, daily glimepiride, and placebo.

RESEARCH DESIGN AND METHODS
Patients with type 2 diabetes receiving metformin were randomized to albiglutide (30 mg), sitagliptin (100 mg), glimepiride (2 mg), or placebo. Blinded dose titration for albiglutide (to 50 mg) and glimepiride (to 4 mg) was based on predefined hyperglycemia criteria. The primary end point was change in HbA1c from baseline at week 104. Secondary end points included fasting plasma glucose (FPG), weight, and time to hyperglycemic rescue.

RESULTS
Baseline characteristics were similar among the albiglutide (n = 302), glimepiride (n = 307), sitagliptin (n = 302), and placebo (n = 101) groups. Baseline HbA1c was 8.1% (65.0 mmol/mol); mean age was 54.5 years. The mean doses for albiglutide and glimepiride at week 104 were 40.5 and 3.1 mg, respectively. At week 104, albiglutide significantly reduced HbA1c compared with placebo (−0.9% [−9.8 mmol/mol]; P < 0.0001), sitagliptin (−0.4% [−4.4 mmol/mol]; P = 0.0001), and glimepiride (−0.3% [−3.3 mmol/mol]; P = 0.0033). Outcomes for FPG and HbA1c were similar. Weight change from baseline for each were as follows: albiglutide −1.21 kg (95% CI −1.68 to −0.74), placebo −1.00 kg (95% CI −1.81 to −0.20), sitagliptin −0.86 kg (95% CI −1.32 to −0.39), glimepiride 1.17 kg (95% CI 0.70–1.63). The difference between albiglutide and glimepiride was statistically significant (P < 0.0001). Hyperglycemic rescue rate at week 104 was 25.8% for albiglutide compared with 59.2% (P < 0.0001), 36.4% (P = 0.0118), and 32.7% (P = 0.1504) for placebo, sitagliptin, and glimepiride, respectively. Rates of serious adverse events in the albiglutide group were similar to comparison groups. Diarrhea (albiglutide 12.9%, other groups 8.6–10.9%) and nausea (albiglutide 10.3%, other groups 6.2–10.9%) were generally the most frequently reported gastrointestinal events.

CONCLUSION
Added to metformin, albiglutide was well-tolerated; produced superior reductions in HbA1c and FPG at week 104 compared with placebo, sitagliptin, and glimepiride; and resulted in weight loss compared with glimepiride.
The management of type 2 diabetes has become an increasingly complex practice given the number of treatments available (1). Despite the availability of new therapeutic agents, many patients with type 2 diabetes continue to have uncontrolled glycemia (2–4), and treatment adherence varies but remains relatively poor (5–9).

Among patients taking metformin but who do not have adequately controlled diabetes, data are limited regarding next-step concomitant treatment (10). As a result, extended head-to-head comparisons of type 2 diabetes medications mirroring treatment algorithms (i.e., combinations with metformin) are needed to aid clinicians in making treatment decisions (11,12). Recent treatment guidelines have positioned incretin-based therapies, such as GLP-1 receptor agonists (GLP-1RAs), as alternative first-line therapies in certain clinical settings and as second-line therapies following metformin because of their substantial effectiveness in improving glycemic control as well as other positive effects, such as weight loss and low hypoglycemia rates (10,13,14).

Albiglutide is a novel, once-weekly, long-acting GLP-1RA composed of a dipeptidyl peptidase-4 (DPP-4)–resistant GLP-1 dimer fused to recombinant human albumin. This structure affords an extended half-life of \( \frac{1}{2} \) day and, as a consequence, once-weekly dosing (15,16). In a multinational phase 2b study of type 2 diabetes, albiglutide 30 mg once-weekly reduced HbA1c by \( 2.08\% \) (29.5 mmol/mol) and also reduced fasting plasma glucose (FPG) and weight, with a low incidence of gastrointestinal (GI) adverse events (AEs) (16).

The HARMONY program for albiglutide includes eight pivotal phase 3 studies designed to evaluate the efficacy and safety of albiglutide compared with placebo, oral antidiabetic medications, insulin glargine, and another GLP-1RA in a typical type 2 diabetes population (17,18). Here, we present 2-year primary end point data for HARMONY 3, which is a 3-year phase 3 study comparing the efficacy and safety of weekly albiglutide with daily sitagliptin, daily glimepiride, and placebo in patients with diabetes receiving metformin but not adequately controlled by the medication.

**RESEARCH DESIGN AND METHODS**

**Study Design**

This was a phase 3, randomized, double-blind, placebo- and active-controlled parallel-group study that occurred between 17 February 2009 and 21 March 2013; the study comprised 4 study periods: screening, run-in/stabilization (4 weeks), treatment (156 weeks; 104-week data are reported here), and posttreatment follow-up (8 weeks) (Fig. 1A); the trial is registered as NCT00838903 at clinicaltrials.gov. Eligible patients were stratified by HbA1c level (\( < 8.0\% \) [\( < 63.9 \) mmol/mol] vs. \( \geq 8.0\% \) [\( \geq 63.9 \) mmol/mol]), history of myocardial infarction (MI), and age (\( < 65 \) vs. \( \geq 65 \) years) and were randomly assigned (3:3:3:1) to receive, in addition to their background metformin, 1 of 4 treatments at baseline: albiglutide 30 mg, sitagliptin 100 mg, glimepiride 2 mg, or placebo. Matching placebos for albiglutide, sitagliptin, and glimepiride were used to maintain blinding to treatment.

After randomization, patients with persistent hyperglycemia qualified to undergo dose titration and/or hyperglycemia rescue. Blinded up-titration of albiglutide from 30 to 50 mg once weekly or glimepiride from 2 to 4 mg once daily occurred if patients exceeded predefined FPG or HbA1c thresholds. The final titration threshold, from week 12 until week 143, was HbA1c 7.5% (58.5 mmol/mol); there was no titration from week 143 to week 156. In general, 4 weeks after up-titration, patients meeting criteria including predefined FPG or HbA1c thresholds could receive hyperglycemic rescue therapy, in addition to study medication, and remain in the trial. Rescue thresholds early in the trial were based...
on FPG (≥280 mg/dL [15.6 mmol/L] from week 2 to week 4; ≥250 mg/dL [13.9 mmol/L] from week 4 to week 12) and, later, on HbA1c (≥8.5% [69.4 mmol/mol] and a ≤0.5% reduction from baseline from week 12 to week 24; ≥8.5% [69.4 mmol/mol] from week 24 to week 104).

**Patients**

**Inclusion Criteria**

Patients were ≥18 years of age, had type 2 diabetes, and were experiencing inadequate glycemic control while taking background metformin (≥1500 mg or maximum tolerated dose) ≥3 months before screening. They also had a baseline HbA1c of 7.0% (53.0 mmol/mol) to 10.0% (85.8 mmol/mol), inclusive; BMI 20 to 45 kg/m²; creatinine clearance >60 mL/min (determined using the Cockcroft-Gault formula); and normal thyroid-stimulating hormone concentration or were clinically euthyroid.

**Exclusion Criteria**

Major exclusion criteria were current ongoing symptomatic biliary disease or history of pancreatitis, recent clinically significant cardiovascular and/or cerebrovascular disease (≥2 months before screening), treated gastroparesis, history of GI surgery thought to signifi-

**Withdrawal Criteria**

Patients withdrew or were removed from the study drug because of loss to follow-up, protocol violation, noncompliance, withdrawal of consent, or an AE or laboratory result requiring withdrawal, including QTc prolongation, elevation of liver function test results, severe potential allergic reactions, confirmed pancreatitis, severe or repeated hypoglycemia, and calcitonin >100 pg/mL.

**Primary and Secondary End Points**

The primary end point was the change in model-adjusted HbA1c from baseline to week 104 between albiglutide and the comparators. Secondary end points included changes in HbA1c, FPG, and weight from baseline over time; the proportion of patients who achieved HbA1c treatment goals (i.e., <6.5% [≤47.5 mmol/mol], <7.0% [≤53.0 mmol/mol], and <7.5% [≤58.5 mmol/mol]); and time to hyperglycemic rescue.

Safety and tolerability were assessed, including AEs and serious AEs (SAEs); safety events of special interest (i.e., GI or hypoglycemic events, injection-site reactions, pancreatitis, thyroid tumors, potential systemic allergic reactions [SARs], and CV events); clinical laboratory evaluations; physical examinations; 12-lead electrocardiograms; vital sign measurements; and immunogenicity.

**Study Conduct**

This study was conducted in accordance with good clinical practice standards, all applicable privacy requirements, and the guiding principles of the Declaration of Helsinki. Written informed consent was obtained from each patient before participation.

**RESULTS**

This study was conducted at 289 centers in 10 countries. Demographics and baseline characteristics were similar among the albiglutide (n = 302), glimepiride (n = 307), sitagliptin (n = 302), and placebo (n = 101) treatment groups (Supplementary Table 1). The mean age for the groups ranged from 54.3 to 56.1 years (84.3% were <65 years old; approximately half of patients were men and the majority were white (63.4–74.5%). Approximately 67.0% of the total population were moderately to severely obese (BMI ≥30 kg/m²); mean weight in all treatment groups ranged from 89.6 to 91.8 kg, and mean duration of diabetes ranged from 5.8 to 6.7 years. In all treatment groups at baseline, HbA1c levels were similar (8.1–8.2% [65.0–66.1 mmol/mol]), as were FPG concentrations (9.0–9.3 mmol/L [162.8–167.4 mg/dL]).

Overall, 67.4% of patients completed active treatment through week 104;
rates of completion were similar among the active treatment groups (sitagliptin 67.7%, glimepiride 68.8%, and albiglutide 68.3%) and lower for the placebo group (59.6%). The main reasons for discontinuing active treatment were withdrawal of consent (placebo 14.4%, sitagliptin 13.1%, glimepiride 13.2%, albiglutide 12.1%) and AEs (placebo 4.8%, sitagliptin 3.2%, glimepiride 4.1%, albiglutide 6.3%). Patient flow is presented in Fig. 1B.

Although all treatment groups went through a blinded up-titration procedure, only the albiglutide and glimepiride groups actually up-titrated to 50 and 4 mg, respectively. By week 104, a higher proportion of patients went through the blinded up-titration process in the placebo (−69%) and sitagliptin (−59%) groups compared with the glimepiride (−54%) and albiglutide (−53%) groups. Mean doses for albiglutide and glimepiride at week 104 were 40.5 and 3.1 mg, respectively.

Primary Outcome: HbA1c
HbA1c reductions from baseline to week 104 were −0.63% (−6.9 mmol/mol) for albiglutide, −0.28% (−3.1 mmol/mol) for sitagliptin, −0.36% (−3.9 mmol/mol) for glimepiride, and +0.27% (3.0 mmol/mol) for placebo. The model-adjusted mean difference (albiglutide vs. comparator treatment) demonstrated that albiglutide, when added to metformin, was clinically and statistically superior to placebo (−0.9% [−9.8 mmol/mol]; 95% CI −1.2 to −0.7; \( P < 0.0001 \)), sitagliptin (−0.4% [−4.4 mmol/mol]; 95% CI −0.5 to −0.2; \( P = 0.0001 \)), and glimepiride (−0.3% [−3.3 mmol/mol]; 95% CI −0.5 to −0.1; \( P = 0.0033 \)) (Fig. 2A). Albiglutide had the most durable effect, with a mean HbA1c of 7.5% (58.5 mmol/mol) at week 104 compared with sitagliptin (7.8% [61.7 mmol/mol]), glimepiride (7.8% [61.7 mmol/mol]), and placebo (8.4% [68.3 mmol/mol]) (Fig. 2B).

More albiglutide-treated patients reached HbA1c treatment thresholds at each level (<6.5% [<47.5 mmol/mol], <7.0% [<53.0 mmol/mol], <7.5% [<58.5 mmol/mol]) compared with placebo, sitagliptin, and glimepiride at week 104 (Supplementary Fig. 1). The difference between albiglutide and the comparators was statistically significant for placebo at all threshold levels (\( P \leq 0.02 \)) and was comparable with only sitagliptin and glimepiride at the 7.5% (<58.5 mmol/mol; \( P \leq 0.04 \)) level. For the albiglutide group, these treatment thresholds were met by 17.1%, 38.6%, and 58.7% of patients, respectively. Subgroup analyses for age, race, ethnicity, sex, baseline BMI, and baseline HbA1c were all consistent with the primary end point (Supplementary Fig. 2).
Secondary Outcomes

**FPG**
Changes in FPG from baseline at week 104 were consistent with the primary end point (Fig. 2C). The treatment group difference (albiglutide – comparator treatment) for a model-adjusted least squares mean decrease from baseline to week 104 demonstrated that, when added to metformin, albiglutide was statistically superior to placebo $(-1.5 \text{ mmol/L} [\pm 28 \text{ mg/dL}]; P < 0.0001)$, sitagliptin $(-0.9 \text{ mmol/L} [\pm 16 \text{ mg/dL}]; P = 0.0002)$, and glimepiride $(-0.6 \text{ mmol/L} [\pm 10 \text{ mg/dL}]; P = 0.0133)$.

**Weight**
At week 104, weight loss occurred among patients taking albiglutide $(-1.21 \text{ kg})$, placebo $(-1.0 \text{ kg})$, and sitagliptin $(-0.86 \text{ kg})$, whereas weight gain occurred in glimepiride patients (+1.17 kg). The treatment difference between albiglutide and glimepiride was statistically significant ($P < 0.0001$) (Fig. 2D).

**Time to Hyperglycemic Rescue**
The albiglutide group had the most durable glycemic control. Per Kaplan-Meier estimates, fewer patients received hyperglycemic rescue in the albiglutide group (25.8%) compared with the placebo (59.2%), sitagliptin (36.4%), and glimepiride groups (32.7%). The difference between baseline and time to rescue with albiglutide was statistically significantly longer compared with sitagliptin ($P = 0.0118$) and placebo ($P < 0.0001$) (Fig. 3).

**General Safety and Tolerability**
For overall safety, the proportion of patients experiencing AEs, SAEs, and AEs leading to withdrawal while receiving therapy was relatively balanced among treatment groups (Table 1). Most AEs were mild or moderate in intensity in all treatment groups. The most frequent AEs (occurring in $>7\%$ of patients taking albiglutide) were upper respiratory tract infection, diarrhea, nausea, injection-site reaction, hypertension, nasopharyngitis, and cough. The type of AEs overall and those occurring before rescue (i.e., before the addition of hyperglycemic rescue medication) were similar, and the majority of AEs occurred before rescue (Supplementary Table 2). The rate of AEs was higher with albiglutide and generally due to the higher rate of injection-site reactions (45 of 100 patient-years for albiglutide vs. 1 of 100 patient-years for placebo). Fewer patients experienced SAEs in the albiglutide group (12.9%) than in the placebo group (15.8%) but were comparable with those who experienced SAEs in the sitagliptin and glimepiride groups (9.9% and 11.7%, respectively). Overall, eight fatal SAEs occurred through week 104 (three each for albiglutide and glimepiride and one each for sitagliptin and placebo); none were considered by the investigators to be related to study medication.

**Events of Special Interest (Through Week 104)**

**GI Events**
GI AEs were experienced by a similar proportion of patients in the albiglutide ($n = 110$; 36.4%) and placebo groups ($n = 38$; 37.6%) and fewer in the sitagliptin ($n = 75$; 24.8%) and glimepiride groups ($n = 85$; 27.7%). Few GI events were severe in intensity (1.0%, 1.3%, 1.3%, and 4.0% for placebo, sitagliptin, glimepiride, and albiglutide, respectively) or led to withdrawal of the study drug (1.0%, 1.0%, 0.7%, and 2.0%, respectively). The most common GI event was diarrhea in the sitagliptin, glimepiride, and albiglutide groups and constipation in the placebo group.

At week 104, nausea event rates were comparable between treatment groups (7.9, 5.3, 3.7, and 9.3 events per 100 patient-years for placebo, sitagliptin, glimepiride, and albiglutide, respectively), even though the incidence was highest in the placebo group (10.9%) compared with sitagliptin (6.6%), glimepiride (6.2%), and albiglutide (10.3%). The incidence and event rate of vomiting over the 104 weeks was (5.6%, 4.4 events per 100 patient-years) in the albiglutide group compared with placebo (1.0%, 0.6 events per 100 patient-years), sitagliptin (4.3%, 3.2 events per 100 patient-years), and glimepiride (3.6%, 2.1 events per 100 patient-years). The per-visit prevalence of nausea/vomiting among patients receiving albiglutide was <5% at each time point (Supplementary Fig. 3).

**Hypoglycemia**
Documented symptomatic hypoglycemia ($\leq3.9 \text{ mmol/L} [\leq70 \text{ mg/dL}]$) before rescue with albiglutide was low (3.0%) and was similar to placebo (4.0%) and sitagliptin (1.7%) compared with glimepiride (17.9%) (Table 1). No severe hypoglycemic events were reported before rescue.

**Injection-Site Reactions**
Events classified by investigators as injection-site reactions occurred more frequently with albiglutide (17.2%; $n = 52$) compared with glimepiride (7.8%; $n = 24$), sitagliptin (6.3%; $n = 19$), and placebo (5%; $n = 5$). Injection-site reactions for albiglutide were mostly mild to
Two patients receiving sitagliptin developed thyroid cancer: one experienced follicular papillary carcinoma on day 48 and the other papillary thyroid cancer on day 549. In these three patients, thyroid cancer diagnoses were considered by the investigator to be not related to the study drug, and calcitonin concentrations were not abnormal.

**Potential SARs**

A search of the standardized Medical Dictionary for Regulatory Activities queries identified two patients (placebo, n = 1; glimepiride, n = 1) who experienced angioedema as an SAE. The investigator considered neither to be related to the study drug but instead related to ACE inhibitor therapy. Both patients remained in the study after discontinuing ACE inhibitor therapy. Neither patient had positive antialbiglutide antibodies, and no other cases of angioedema, anaphylaxis, pharyngeal edema, or laryngeal edema occurred. The investigators did not flag any additional events of interest.

**Immunogenicity**

Antialbiglutide antibody incidence among albiglutide-treated subjects was 7.0% (21 of 302 subjects), and included 1 subject (0.4%) with preexisting antibodies (positive at baseline). Antibodies were nonneutralizing and showed reactivity with GLP-1 in 16 of the 21 antibody-positive subjects and with albumin in 5 antibody-positive subjects. No samples tested positive for antialbiglutide IgE antibodies, and no SARs were reported for antibody-positive subjects.

**Cardiovascular Parameters**

At baseline, lipids and blood pressure were well controlled and mean values were similar across the four treatment groups (Supplementary Table 3). There were no clinically meaningful mean changes to lipids throughout the study. Minor changes in SBP and DBP, respectively, from baseline occurred in all treatment groups at week 104: placebo (2.2 and 0.5 mmHg), sitagliptin (0.2 and 0.7 mmHg), glimepiride (0.9 and 1.0 mmHg), and albiglutide (−0.5 and −0.7 mmHg). Treatment differences in SBP and DBP at week 104 between albiglutide and the three comparators were not statistically significant. Similarly, there were no meaningful changes from baseline at week 104 in mean heart rate: placebo, 2.3 bpm; sitagliptin, 0.8 bpm; glimepiride, −0.5 bpm; and albiglutide, 1.3 bpm.

**CONCLUSIONS**

When added to metformin, albiglutide produced clinically and statistically superior and more sustained reduction in HbA1c at week 104 compared with...
placebo, sitagliptin, and glimepiride. The sustained treatment effect of albiglutide also is supported by the time to hyperglycemic rescue, which showed that fewer subjects taking albiglutide required rescue by week 104 compared with patients treated with placebo, sitagliptin, and glimepiride; the difference was statistically significant for albiglutide versus placebo and sitagliptin. Interestingly, the reduction in HbA1c was similar during the early treatment period (~4 weeks). This might not have been anticipated given the longer time to a steady state for the once-weekly albiglutide and the quick mechanism of action of sulfonylureas. Similar clinically and statistically superior results with albiglutide compared with all other treatment arms were observed for change in FPG from baseline and the proportion of patients meeting clinically relevant HbA1c treatment goals. In addition, patients receiving albiglutide, sitagliptin, and placebo lost weight through week 104, whereas patients treated with glimepiride gained weight; the difference between albiglutide and glimepiride was statistically significant (P < 0.0001).

The sustained effect of diabetes therapy is a critical clinical issue. Previous type 2 diabetes comparator trials have demonstrated the superiority or noninferiority of GLP-1RAs with or without metformin but have been shorter 26-week trials (20–22). The Diabetes Therapy Utilization: Researching Change in A1C, Weight, and Other Factors Through Intervention with Exenatide Once-Weekly (DURATION)-2 and Liraglutide Intervention with Exenatide Once-weekly trials (20–22) included data after rescue. These design features, however, may have complicated the interpretation of some results.

In conclusion, when added to metformin, albiglutide produced clinically and statistically significant reductions in HbA1c and FPG at week 104 compared with placebo, sitagliptin, and glimepiride. Patients receiving albiglutide, sitagliptin, and placebo lost body weight through week 104, whereas patients taking glimepiride gained weight; the difference between albiglutide and glimepiride was statistically significant. Albiglutide was generally well tolerated, and rates of SAEs were similar across treatment groups. The most frequent AEs for albiglutide were largely consistent with the known profile for GLP-1RAs.

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or principal investigator for Amylin, AstraZeneca, Eli Lilly and Company, GlaxoSmithKline, Merck & Co., Inc., Medtronic Inc., Novo Nordisk, Proctor & Gamble Co., Prodigy Diabetes Care, Sanofi, and Tethys, some of which are companies producing GLP-1RAs or DPP-4 inhibitors. M.N.F. also has served as a consultant for GlaxoSmithKline, Pfizer, and Proctor & Gamble Co. No other potential conflicts of interest relevant to this article were reported.

The sponsor of the study participated in the study design, data collection, data review, data analysis, and writing of the report. All authors had full access to all the data in the study. The corresponding author reviewed the trial report (signatory investigator), had full access to all data in the study, and had final responsibility for the decision to submit for publication.

**Author Contributions.** B.A. and M.N.F. provided study patients. S.L.J., M.S., D.T.C., F.Y., and C.P. analyzed and interpreted data. B.A., S.L.J., D.T.C., F.Y., and M.N.F. wrote and revised the manuscript. F.Y. performed the statistical analysis. All authors revised the manuscript, reviewed the final manuscript, and approved the manuscript for submission. M.N.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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