Title: Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease: A double-blind, randomised controlled trial.

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ABSTRACT

Background: Glucagon-like peptide 1 agonists differ in chemical structure, duration of action and in their effects on clinical outcomes. The cardiovascular effects of once-weekly albiglutide in type 2 diabetes are unknown.

Methods: We randomly assigned patients with type 2 diabetes and cardiovascular disease to the addition of once-weekly subcutaneous injection of albiglutide (30 mg to 50 mg) or matching placebo to standard care. We hypothesized that albiglutide would be noninferior to placebo for the primary outcome of first occurrence of cardiovascular death, myocardial infarction, or stroke. If noninferiority was confirmed by an upper limit of the 95% confidence interval for the hazard ratio of less than 1.30, closed-testing for superiority was prespecified.

Findings: Overall, 9463 participants were followed for a median of 1.6 years. The primary composite outcome occurred in 338 of 4731 patients (7.1%; 4.6 events per 100 person-years) in the albiglutide group and in 428 of 4732 patients (9.0%; 5.9 events per 100 person-years) in the placebo group (hazard ratio, 0.78; 95% confidence interval [CI], 0.68 to 0.90), indicating that albiglutide, was superior to placebo ($P<0.0001$ for noninferiority, $P=0.0006$ for superiority).

The incidence of acute pancreatitis (albiglutide 10 patients and placebo 7 patients), pancreatic cancer (6 and 5), medullary thyroid carcinoma (0 and 0), and other serious adverse events did not differ significantly between the two groups.

Interpretation: In patients with type 2 diabetes and cardiovascular disease, albiglutide was superior to placebo with respect to major adverse cardiovascular events.

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Research in context

Evidence before this study

We searched PubMed for reports of randomised trials assessing the effects of glucagon-like peptide 1 agonists on cardiovascular outcomes published in English up to August 1, 2018, using the search terms “glucagon-like peptide 1 agonist or analogue”, “GLP-1 receptor agonist or analogue”, “exenatide”, “lixisenatide”, “semaglutide”, “liraglutide”, “exenatide”, “dulaglutide”, “taspoglutide”, “albiglutide”, “cardiovascular outcomes”, and “diabetes”. Four cardiovascular outcome trials were identified. The LEADER trial included 9340 patients with type 2 diabetes and cardiovascular disease or cardiovascular risk factors which were followed for a median of 3.8 years. Patients were randomised to placebo or once-daily liraglutide, structurally homologous to native GLP-1, added to standard care. Liraglutide reduced the primary endpoint composite of major adverse cardiovascular events (MACE) consisting of cardiovascular death, myocardial infraction or stroke (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P = 0.01 for superiority). Semaglutide, also structurally homologous to native GLP-1, was studied in 3297 similar participants in the SUSTAIN-6 trial which showed that, over a median of 2.1 years, once-weekly semaglutide was noninferior to placebo for MACE (HR, 0.74; 95%CI, 0.58 to 0.95; P<0.001 for noninferiority). The ELIXA trial included 6068 patients with type 2 diabetes and a recent acute coronary syndrome which were followed for a median of 2.1 years. Patients were randomised to placebo or lixisenatide once daily, an exendin-4 based GLP-1 receptor agonist, added to standard care. Lixisenatide was non-inferior to placebo for the primary composite outcome of MACE plus unstable angina (HR, 1.02; 95%CI, 0.89 to 1.17; P<0.001 for noninferiority). The EXSCEL trial included 14,752 patients with type 2 diabetes and cardiovascular disease or cardiovascular risk factors which were followed for a median of 3.2 years. Patients were randomised to placebo or exenatide once weekly, an exendin-4 based GLP-1 receptor agonist, added to standard care. Exenatide was non-inferior to placebo for the primary composite outcome of MACE (HR, 0.91; 95%CI, 0.83 to 1.00; P<0.001 for

noninferiority; P = 0.06 for superiority). There seems to be variation in the results of existing trials with GLP-1 receptor agonists, which if correct, might reflect drug structure or duration of action, patients studied, duration of follow-up or other factors.

Added value of this study

The results of the Harmony Outcomes trial showed that albiglutide, the GLP-1 receptor ligand of which is structurally homologous with native GLP-1, administered once-weekly over a median period of 1.6 years, reduced the risk of MACE when added to standard care in patients with type 2 diabetes and cardiovascular disease. The totality of evidence suggests that GLP-1 receptor agonists reduce the risk of athero-thrombotic events in patients with type 2 diabetes and high cardiovascular risk.

INTRODUCTION

The risk of fatal and nonfatal cardiovascular events is much higher in people with type 2 diabetes than in the general population.[1,2] Agents in two classes of newer glucose-lowering therapies, the sodium-glucose cotransporter 2 (SGLT-2) inhibitors and the glucagon-like peptide-1 (GLP-1) receptor agonists, have been shown to reduce the risk of major adverse cardiovascular events, although the findings with the latter treatments have been inconsistent.[3-8] Specifically, not all tested GLP-1 receptor agonists reduced cardiovascular events and the effect on individual cardiovascular outcomes varied between the effective agents.[5-8] Liraglutide and semaglutide, with structural homology to native GLP-1, reduced cardiovascular events whereas there was no benefit with the exendin-4 based agents lixisenatide and exenatide.[5-8] In addition to differences in chemical structure and potency, these treatments also differ markedly in duration of action and were studied in different patient populations and in trials of different design, size and duration of follow-up.[5-8] Consequently, there remains uncertainty about the cardiovascular effects of GLP-1 receptor agonists as a class.

Albiglutide is a GLP-1 receptor agonist generated through genetic fusion of 2 tandem copies of modified human GLP-1 (97% amino acid sequence homology to endogenous human GLP-1 fragment 7-36) to human albumin and is sufficiently long-acting to be injected weekly.[9,10] In accordance with regulatory guidance, we assessed the cardiovascular safety and efficacy of albiglutide in Harmony Outcomes, a trial which included patients with type 2 diabetes and cardiovascular disease.[11]

METHODS

TRIAL OVERSIGHT

We conducted this randomized, double-blind, placebo-controlled, event-driven trial at 610 sites in 28 countries.[11] The protocol was approved by the ethics committee at each participating site and all patients provided written informed consent. An independent data and safety monitoring committee, with access to unblinded data, performed regular safety surveillance.

TRIAL POPULATION

Men and women aged 40 years or older with a diagnosis of type 2 diabetes and established disease of the coronary (myocardial infarction, ⩾50% stenosis in ⩾1 coronary artery, or prior coronary revascularisation), cerebrovascular (ischaemic stroke, ⩾50% carotid artery stenosis, or carotid vascular procedure), or peripheral arterial circulation (intermittent claudication and ankle:brachial index <0.9, non-traumatic amputation, or peripheral vascular procedure) who had a glycated haemoglobin level more than 7.0% (53 mmol per mole) were eligible for participation in the trial.

Key exclusion criteria were estimated glomerular filtration rate [eGFR] less than 30 ml per minute per 1.73 m^2 of body-surface area, severe gastroparesis, prior pancreatitis or significant risk factors for pancreatitis, a personal or family history of medullary carcinoma of the thyroid or multiple endocrine neoplasia type 2, history of pancreatic neuroendocrine tumour, or current use of a GLP-1 receptor agonist. A complete list of trial inclusion and exclusion criteria is provided in the protocol.

Patients were assigned in a 1:1 ratio to receive subcutaneous injections of albiglutide or matching placebo once weekly, according to a sequestered, fixed, randomisation schedule. Investigators used an interactive voice or web response system to obtain treatment

assignment. The starting dose of study medication was 30 mg once weekly. If, after at least 5 weeks of study treatment, the investigator determined that a trial participant required intensification of glucose-lowering therapy, the dose of study treatment could be increased to 50 mg; the dose could be decreased back to 30 mg if 50 mg was not tolerated. If the glycaemic goal determined by the investigator was not met following increase in dose of study medication, other glucose-lowering medications could be adjusted or added (except for a GLP-1-receptor agonist). Protocol-specified reasons for discontinuation of trial medication included occurrence of pancreatitis, pancreatic cancer, medullary carcinoma of the thyroid or thyroid C-cell neoplasia, severe hypersensitivity reactions attributable to study medication, pregnancy, eGFR less than 15 ml per minute per 1.73 m^2 of body-surface area, kidney dialysis or transplantation, or liver chemistry abnormalities exceeding protocol-specified thresholds.[11]

OUTCOMES

The primary outcome was defined as the first occurrence of any component of the composite outcome of death from cardiovascular causes, myocardial infarction, or stroke. Secondary cardiovascular outcomes included a four-component composite (the primary composite with the addition of urgent revascularisation for unstable angina), the individual components of the primary end point, and the composite of cardiovascular death or hospitalisation due to heart failure. Secondary metabolic end points included time to initiation of chronic insulin therapy, time to first occurrence of an important microvascular event, changes in glycated haemoglobin and weight, and proportion of participants achieving glycaemic control without severe hypoglycaemia and with a gain of less than 5% of body weight by the end of the study. Safety end points included change in blood pressure and heart rate, change in eGFR, and adverse events of special interest including, development of specified malignancies

(medullary thyroid cancer, pancreatic cancer and haematological malignancies), pancreatitis, severe hypoglycaemia, injection site reactions, immunological reactions, diabetic retinopathy, worsening renal function and death from any cause. A complete list of end points is included in the protocol. An independent clinical events classification committee whose members were unaware of the trial-group assignments adjudicated all the components of the primary composite outcome, secondary cardiovascular outcomes and death; these events are defined in the Clinical Event Definitions section in the Supplementary Appendix. A separate expert committee adjudicated suspected cases of pancreatitis.

STATISTICAL ANALYSIS

The primary objective of the trial was to investigate the effect of albiglutide, compared with placebo, on the primary outcome, testing first for noninferiority and, if the pre-specified criterion for non-inferiority was met, then for superiority. We used a closed testing procedure and therefore no adjustment of the significance level was required for testing of superiority.[12] Consistent with regulatory guidance, noninferiority would be declared if the upper limit of the two-sided 95% confidence interval of the hazard ratio was less than 1.30, and superiority established if the upper limit was less than 1.00.[13, 14]

Assuming a true hazard of 1.00, we estimated that 611 events would be needed to have 90% power for the test of noninferiority. An event rate in the range of 2.0% to 3.0% per year was estimated for the primary end point, based on the results of prior trials, meaning that the target 611 events could be attained by following approximately 9400 patients for an average of 2.2 to 3.2 years. After the trial began, the blinded aggregate event rate was observed to be higher than anticipated, and, therefore, accrual of 611 events would occur over a much shorter period (potentially as short as a median of 1.1 years). To ensure adequate exposure for

evaluation of safety, the protocol was revised to require follow-up for a median of at least 1.5 years in addition to the occurrence of at least 611 primary events.

The time-to-event analyses of the primary and secondary cardiovascular outcomes were performed in the intention-to-treat population using Cox proportional hazards regression, with treatment group as the only explanatory variable.[13] The Kaplan–Meier method was used to estimate event rates. These analyses included all patients randomly assigned to study treatment, whether taken or not, and followed to the study closure visit (or final date vital status could be ascertained). No adjustment for multiplicity was prespecified for the secondary and other endpoints and only 95% confidence intervals are provided.[12]

The primary composite outcome was analysed in prespecified subgroups that were defined by baseline characteristics, including age at randomisation; sex; race/ethnicity; geographic region; type of glucose-lowering therapy (insulin, metformin and dipeptidyl peptidase-4 inhibitor); duration of diabetes; history or no history of coronary artery disease, cerebrovascular disease, or peripheral arterial disease and combinations of these; history or no history of heart failure; use of statin or antiplatelet therapy; history of smoking; body-mass index; glycated haemoglobin level; eGFR.

The safety analyses were performed in patients who underwent randomisation and received at least one dose of albiglutide or placebo.

Baseline characteristics were summarised as means and standard deviations, medians and ranges, or percentages. Longitudinal measures, such as glycated haemoglobin level and body weight, were analysed using mixed model for repeated measurements, and the least-squares mean differences between treatment-groups were estimated, together with 95% confidence intervals. Analyses were performed using SAS software, version 9.4 (SAS Institute).

Role of the funding source

The trial protocol was developed by the members of the Executive Committee in conjunction with Duke Clinical Research Institute and the sponsor, GlaxoSmithKline Research and Development Ltd. These parties were also responsible for oversight of trial. Details of the trial organisation and a complete list of the investigators are provided in the Supplementary Appendix. The statistical analyses were performed by a contract research organisation on behalf of the sponsor, according to a prespecified plan, and corroborated by Duke Clinical Research Institute. The statistical analysis plan is available in the Supplementary Appendix. All the authors had access to the final trial results and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. The manuscript, drafted by the corresponding author, was revised and approved by all the authors, who assume responsibility for its accuracy and completeness and made the decision to submit the manuscript for publication.

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RESULTS

TRIAL CONDUCT

A total of 9463 patients underwent randomisation between 1 July 2015 and 7 December 2016 and were included in the intention-to-treat analysis; 4731 were assigned to receive albiglutide and 4732 to receive placebo. Starting 8 November 2017, when it was projected that 611 primary endpoints and a median follow-up of at least 1.5 years had accrued, subjects returned for a final visit and discontinuation from study treatment, with trial completion in March 2018. The actual median duration of follow-up was 1.6 years (interquartile range, 1.3 to 2.0; maximum, 2.6) for the primary outcome. Vital status was not known for 61 of 9463 participants (0.6%) (Figure 1). A total of 24% of patients assigned to albiglutide and 27% of patients assigned to placebo discontinued study medication prematurely for reasons other than death. Study treatment was taken for 87% of the total follow-up time for cardiovascular outcomes in the albiglutide group and 85% of that time in the placebo group. Among patients who received at least one dose of albiglutide or placebo, 2371 of 4717 patients (50.3%) in the albiglutide group were taking the maximum dose of 50 mg at the time of their last recorded dose, and 2982 of 4715 patients (63.2%) in the placebo group were taking the volume-matched equivalent.

PATIENTS

The demographic and clinical characteristics of the patients were similar in the two groups (Table 1). The mean age of the participants was 64.1 years and 30.6% were women. The mean duration of diabetes was 14.1 years, the mean eGFR was 79 ml per minute per 1.73 m^2, and the mean glycated haemoglobin level was 8.7% (standard deviation, 1.5).

Among the participants, 6678 (70.6%) had a history of coronary artery disease, 2354 (24.9%) peripheral artery disease, 2342 (24.7%) cerebrovascular disease and 1922 (20.3%) had a history

of heart failure. Patients received standard therapies for diabetes and cardiovascular disease (Table 1).

PRIMARY AND SECONDARY OUTCOMES

The primary composite endpoint occurred in 338 of 4731 patients (7.1%; 4.57 events per 100 person-years) in the albiglutide group and in 428 of 4732 patients (9.0%; 5.87 events per 100 person-years) in the placebo group (hazard ratio, 0.78; 95% CI, 0.68 to 0.90), indicating that albiglutide was both non-inferior to placebo for cardiovascular safety (P<0.001 for non-inferiority) and superior to placebo for efficacy (P<0.001 for superiority) (Table 2 and Figure 2). The hazard ratios (95% confidence intervals) for each of the components of the composite were: death from cardiovascular causes 0.93 (0.73 – 1.19), myocardial infarction 0.75 (0.61 – 0.90) and stroke 0.86 (0.66 – 1.14) (Table 2 and Figure 2). Subgroup analyses are shown in Figure 3. Three of nineteen showed a nominally statistically significant interaction.

The effects of albiglutide on the other secondary cardiovascular outcomes were consistent with its effect on the primary outcome (Table 2). The hazard ratio for death from any cause was 0.95; 95% CI, 0.79 to 1.16.

CHANGES IN METABOLIC MEASURES

Mean glycated haemoglobin decreased more with albiglutide, compared with placebo (difference from placebo at 8 months -0.63, 95% CI -0.69 to -0.58; at 16 months -0.52, 95% CI -0.58 to -0.45) [Figure 4]. Body weight decreased more with albiglutide, compared with placebo (difference from placebo at 8 months –0.66, 95% CI, -0.83 to -0.49 kg; at 16 months –0.83, 95% CI, –1.06, –0.60). New treatment with insulin (taken for more than three months) was started in 107 patients (5.7%) in the albiglutide group and 257 patients (12.9%) in the placebo group (hazard ratio 0.42; 95% CI, 0.33 to 0.53, P<0.001). Other glucose lowering

therapies were added more often in the placebo group than in the albiglutide group (Supplementary Appendix).

SAFETY

Prespecified safety outcomes of special interest are shown in Table 3. The number of injection site reactions was greater in the albiglutide group than the placebo group (86 and 29 patients, respectively), though the number of patients with suspected hypersensitivity reactions was similar in the two groups (45 and 48). Severe hypoglycaemia was less common in the albiglutide group than in the placebo group (31 and 55 patients). Other than for metabolism-related events which were less common in the albiglutide group, there were no clinically meaningful differences in serious adverse events between treatment groups (Supplementary Appendix). There was one lower-limb amputation in the albiglutide group and two in the placebo group. A total of 409 (8.6%) of patients assigned to albiglutide and 307 (6.5%) of patients assigned to placebo discontinued study medication prematurely because of an adverse event.

Mean systolic blood pressure decreased slightly more in albiglutide compared with placebo (difference at 8 months -0.65, 95% CI -1.27 to -0.03, and at 16 months -0.67, 95% CI -1.40 to 0.06 mmHg) [Figure 4]. Heart rate increased more on albiglutide compared with placebo (difference at 8 months 1.3, 95% CI 0.9 to 1.6, and at 16 months 1.4, 95% CI 1.00 to 1.9 beats per minute) [Supplementary Appendix]. The difference in eGFR between albiglutide and placebo at 8 months was -1.11, 95% CI -1.84 to -0.39 and at 16 months -0.43, 95% CI -1.26 to +0.41 (Figure 4).

DISCUSSION

In patients with type 2 diabetes and cardiovascular disease receiving standard care, addition of once-weekly albiglutide reduced the risk of the primary composite outcome - death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke – by 22%, compared with the addition of placebo. Overall, the number of patients who would need to be treated to prevent one event over a median of 1.6 years was 50.

All three components of the primary outcome, which were prespecified secondary outcomes, showed point estimates of an effect suggesting benefit, although only that for myocardial infarction was nominally statistically significant. Comparing our findings to trials evaluating other GLP-1-receptor agonists, the effects observed were consistent with the benefits of liraglutide and semaglutide but appear greater than those of lixisenatide and exenatide.[5-8] Whether there are real differences among the findings of the trials conducted is uncertain. A number of factors including the specific molecule and dose tested, differences in the patients randomized, duration of follow-up, and adherence, could account for the apparent variation in results. However, this question can only be properly resolved by head-to-head comparisons between drugs and a recent meta-analysis showed only moderate heterogeneity between the between the prior trials which was not statistically significant.[5-8, 16, 17]

We did not see a statistically significant reduction in death from cardiovascular causes, as seen in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER).[5] However, we observed a delay between the initiation of treatment and the emergence of benefit, as was seen in earlier trials with GLP-1-receptor agonists, and the magnitude of the risk reduction for the primary outcome appeared to increase over time.[5-8] The median follow-up in our trial was considerably shorter than the 3.8 years in LEADER and it may be that an effect on death from cardiovascular causes requires time to accrue.

The effect of albiglutide was consistent across most subgroups analysed, although three of the nineteen examined suggested some heterogeneity in the effect of treatment. Given the lack of a biologically plausible explanation for this, and the absence of similar interactions in other trials using GLP-1-recpetor agonists, we believe that our findings probably reflect the play of chance, related to the large number of subgroups analysed.

The point estimate for another secondary outcome, death from cardiovascular causes or heart failure hospitalisation, also favoured albiglutide but was not statistically significant. This is clinically relevant, given concerns about increased risk of heart failure with certain other glucose-lowering therapies[18].

The benefit of albiglutide was evident in patients who were well treated with other effective cardiovascular therapies. Despite no major difference between randomised treatment groups in blood pressure, body weight, or renal function over time, treatment with albiglutide reduced the risk of major cardiovascular events over a relatively short period of follow-up. The mean glycated haemoglobin level at baseline was 8.7% and was reduced by approximately 1% at four months in the albiglutide group, compared with placebo, and remained lower in the albiglutide group for the duration of the trial, despite a decrease over time in glycated haemoglobin in the placebo group. Other glucose-lowering therapies, including SGLT2 inhibitors and insulin, were added more commonly in patients the placebo group, compared with the albiglutide group. The exact reasons why GLP-1 receptor agonists reduce athero-thrombotic events is unknown but putative, potentially beneficial, cardiovascular actions have been described.[19]

The only prespecified adverse event of interest that was significantly more common in the albiglutide group was injection-site reaction, although this occurred in less than two percent of patients. Severe hypoglycaemia was uncommon overall and occurred less frequently in the albiglutide group than in the placebo group, probably due, in part, to the greater use of insulin

and other glucose-lowering therapies in the placebo group. There was no excess of reported new or worsening retinopathy in the albiglutide group.[20, 21] Only serious adverse events were collected in addition to the prespecified adverse events of interest and these did not show any difference between albiglutide and placebo for non-metabolism-related events. Overall, albiglutide was discontinued slightly less frequently than placebo, although it should be noted that, by design, our trial did not require forced up-titration of the dose of study drug.[11]

One strength of our trial was that, except for GLP-1-receptor agonists, investigators were free to use any other glucose-lowering therapy, including dipeptidyl peptidase 4 inhibitors and SGLT2 inhibitors. The inclusion and exclusion criteria ensured a high rate of cardiovascular events. Our trial also has some limitations, including the relatively short duration of follow-up, and lack of measurement of lipids and urinary albumin excretion. We did not collect detailed information on microvascular complications. Although the short overall duration of follow-up might raise concerns about identification of longer-term safety problems, prior studies with albiglutide collected information on safety and tolerability for up to 3 years. About one quarter of patients discontinued study treatment but this appears in line with discontinuation rates in other trials using GLP-1-receptor agonists and study treatment was taken for approximately 86% of total follow-up time for cardiovascular outcomes

In summary, when added to standard care in patients with type 2 diabetes and established cardiovascular disease, the long-acting GLP-1-receptor agonist albiglutide reduced the risk of major adverse cardiovascular events with acceptable tolerability and safety. These findings provide more evidence that certain GLP-1-receptor agonists can improve cardiovascular outcomes in patients with type 2 diabetes.[21-23]

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Contributions

AFH, JBG, SJ, RD'A, NPJ, LAL, AER, JMcM and SDP contributed to the design of the study. KNS and MCS analysed the data. AFH, JBG, SJ, RD'A, CBG, NPJ, LAL, KNS, MCS, KMT, JMcM and SDP interpreted the data. JMcM drafted the report which was critically revised by AFH, JBG, SJ, RD'A, CBG, NPJ, LAL, KNS, MCS, KMT, JMcM and SDP. All authors have read and approved the final version.

Declarations of interest

AFH: Grants to the institution from AstraZeneca, GlaxoSmithKline, Luitpold, Novartis, Merck, Portola Pharmaceuticals, Verily. Has been consultant to AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Novartis, Merck.

JBG: Grants to the institution from AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline. Has been consultant to: AstraZeneca, Boehringer Ingelheim, NovoNordisk, Merck

SJ is a GlaxoSmithKline employee and shareholder.

RD'A: Consultant to GlaxoSmithKline (for Harmony-Outcomes trial).

CBG: Grants to the institution from Apple, Armetheon, Daiichi-Sankyo, FDA, grants to the institution from and consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Medtronic, NIH, Novartis, Pfizer, and consultancy

fees from Abbvie, Boston Scientific, Gilead Sciences, Medscape, Merck, Novo Nordisk, Rho, Roche Diagnostics, Sirtex, and Verseon.

NPJ: GlaxoSmithKline employee and shareholder.

LAL: Grants to the institution from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, Sanofi. Honoraria for presentations: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Servier. Advisory boards for: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Servier.

AER: Grants to the institution from GlaxoSmithKline.

KNS: Grants to the institution from GlaxoSmithKline, Behring.

MCS: Former employee of and shareholder in GlaxoSmithKline and is currently an employee of PAREXEL International.

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REFERENCES

1. Rawshani A, Rawshani A, Franzén S, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. N Engl J Med 2017; 376:1407-1418.

2. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011; 364:829-841.

3. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117-28.

4. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377:644-657.

5. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2016; 375:311-22.

6. Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2016; 375:1834-1844.

7. Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med 2015; 373:2247-57.

8. Holman RR, Bethel MA, Mentz RJ, et al; EXSCEL Study Group. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2017; 377:1228-1239.

9. Tahrani AA, Barnett AH, Bailey CJ. Pharmacology and therapeutic implications of current drugs for type 2 diabetes mellitus. Nat Rev Endocrinol 2016; 12:566-92.

10. Fisher M, Petrie MC, Ambery PD, Donaldson J, Ye J, McMurray JJ. Cardiovascular safety of albiglutide in the Harmony programme: a meta-analysis. Lancet Diabetes Endocrinol 2015; 3:697-703.

11. Green JB, Hernandez AF, D'Agostino RB, et al. Harmony Outcomes: A randomized, double-blind, placebo-controlled trial of the effect of albiglutide on major cardiovascular events in patients with type 2 diabetes mellitus Rationale, design, and baseline characteristics. Am Heart J 2018; 203: 30-38.

12. Dmitrienko A, D'Agostino RB Sr. Multiplicity Considerations in Clinical Trials. N Engl J Med. 2018; 378: 2115-2122.

13. Department of Health and Human Services. Guidance for industry: diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. December 2008 (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf).

14. Mauri L, D'Agostino RB Sr. Noninferiority Trials. N Engl J Med. 2018 ; 378: 304-305.

15. Cox DR. Regression models and life tables (with discussion). J R Stat Soc [Ser B] 1972; 34:187-220.

16. Boyle JG, Livingstone R, Petrie JR. Cardiovascular benefits of GLP-1 agonists in type 2 diabetes: a comparative review. Clin Sci (Lond). 2018; 132: 1699-1709.

17. Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, Pagidipati NJ, Chan JC, Gustavson SM, Iqbal N, Maggioni AP, Öhman P, Poulter NR, Ramachandran A, Zinman B, Hernandez AF, Holman RR; EXSCEL Study Group. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes Endocrinol. 2018; 6: 105-113.

18. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol. 2014; 2: 843-51.

19. Rizzo M, Nikolic D, Patti AM, Mannina C, Montalto G, McAdams BS, Rizvi AA, Cosentino F. GLP-1 receptor agonists and reduction of cardiometabolic risk: Potential underlying mechanisms. Biochim Biophys Acta. 2018 Sep;1864 (9 PtB):2814-2821.

20. Vilsbøll T, Bain SC, Leiter LA, Lingvay I, Matthews D, Simó R, Helmark IC, Wijayasinghe N, Larsen M. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab.; 20: 889-897.

21. Leiter LA, Nauck MA. Efficacy and Safety of GLP-1 Receptor Agonists Across the Spectrum of Type 2 Diabetes Mellitus. Exp Clin Endocrinol Diabetes. 2017; 125: 419-435.

22. Abdul-Ghani M, DeFronzo RA, Del Prato S, Chilton R, Singh R, Ryder REJ. Cardiovascular Disease and Type 2 Diabetes: Has the Dawn of a New Era Arrived? Diabetes Care. 2017; 40: 813-820.

23. Lingvay I, Leiter LA. Use of GLP-1 RAs in Cardiovascular Disease Prevention: A Practical Guide. Circulation. 2018; 137: 2200-2202.

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Table Legends

Table 1. Characteristics of the Patients at Baseline.

Table 2. Primary and Secondary Cardiovascular Outcomes.

Table 3. Adverse Events of Special Interest.

Figure Legends

Figure 1. Enrollment, Follow-up, and Vital Status

ITT = intention-to-treat MACE = major adverse cardiovascular events

Figure 2. Cardiovascular Outcomes

The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, or stroke. The cumulative incidences of the primary outcome and its components were estimated with the use of the Kaplan–Meier method and hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, with treatment with albiglutide or placebo as the sole explanatory variable. Analyses are based upon all participants who underwent randomisation. The displays are truncated at the point where less than 10% of patients remains at risk. The inset in each panel shows the same data on an enlarged y axis.

Figure 3. Primary Composite Outcome According to Prespecified Subgroups.

Race or ethnic group was reported by the patient. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. Cerebrovascular disease included any of stroke, ≥50% carotid artery stenosis or carotid arterial procedure. DPP-4 denotes dipeptidyl peptidase 4, and GFR glomerular filtration rate. HbA1c = glycated haemoglobin. P values for homogeneity for between-group differences were obtained by fitting interaction terms, with no adjustment for multiple testing.

Figure 4. Effects of once-weekly albiglutide

Shown are the effects of once-weekly administration of albiglutide on glycated haemoglobin levels, body weight, systolic blood pressure, and estimated glomerular filtration rate. Overall least-squares mean differences were estimated from the model that included only the patients in whom a baseline value and at least one postbaseline value were obtained.

606 **Table 1. Characteristics of the Patients at Baseline.**

607

	Albiglutide (N=4731)	**Placebo (N=4732)**
Age -yr	64.1 ± 8.7	64.2 ± 8.7
Female sex – no. (%)	1427 (30.2)	1467 (31.0)
Race/ethnicity (%)		
Non-Hispanic White	3295 (69.7)	3288 (69.5)
Asian	228 (4.8)	242 (5.1)
Non-Hispanic Black or African-American	111 (2.4)	114 (2.4)
Hispanic	1005 (21.2)	988 (20.9)
Other	92 (1.9)	100 (2.1)
Geographic region – no. (%)		
Western Europe	1684 (35.6)	1708 (36.1)
Eastern/Central Europe	1037 (21.9)	1010 (21.3)
North America	967 (20.4)	978 (20.7)
Latin America	858 (18.1)	845 (17.9)
Asia Pacific	185 (3.9)	191 (4.0)
Current smoking – no. (%)	737 (15.6)	751 (15.9)
Medical history – no. (%)		
Coronary artery disease[#]	3333 (70.5%)	3345 (70.7%)
Hypertension	4089 (86.4)	4095 (86.5)
Myocardial infarction	2223 (47.0)	2236 (47.3)
Coronary artery bypass surgery	890 (18.8)	842 (17.8)
Percutaneous coronary intervention	2050 (43.3%)	2113 (44.7%)

Stroke	827 (17.5)	854 (18.0)
Peripheral artery disease	1195 (25.3)	1159 (24.5)
Heart failure	954 (20.2)	968 (20.5)
Atrial fibrillation	394 (8.3%)	392 (8.3%)
Body-mass index – kg/m^2	32.3 ± 5.9	32.3 ± 5.9
Blood pressure - mmHg		
Systolic	134.8 ± 16.6	134.7 ± 16.5
Diastolic	76.8 ± 10.1	76.8 ± 10.1
Glycated haemoglobin - %	8.76 ± 1.5	8.72 ± 1.5
eGFR - $ml/min/1.73m^2$	79.1 ± 25.6	78.9 ± 25.4
Duration of diabetes - yr	14.1 ± 8.6	14.2 ± 8.9
History of microvascular disease – no. (%)		
Diabetic eye disease	982 (20.8)	955 (20.2)
Nephropathy	898 (19.0)	840 (17.8)
Peripheral Sensory Neuropathy	1562 (33.0)	1533 (32.4)
Autonomic Neuropathy	143 (3.0)	107 (2.3)
Cardiovascular medications – no. (%)		
Beta-blocker	3128 (66.1)	3182 (67.2)
Calcium-channel blocker	1428 (30.2)	1431 (30.2)
ACE inhibitor	2263 (47.8)	2353 (49.7)
Angiotensin receptor blocker	1599 (33.8)	1511 (31.9)
Thiazide diuretic	1089 (23.0)	1037 (21.9)
Loop diuretic	895 (18.9)	899 (19.0)
Statin	3967 (83.9)	3988 (84.3)

Aspirin	3652 (77.2)	3639 (76.9)
P2Y12 inhibitor	1224 (25.9)	1251 (26.4)
Glucose-lowering medications – no. (%)		
None/diet	42 (0.9)	35 (0.7)
Biguanide	3463 (73.2)	3506 (74.1)
Sulfonylurea	1346 (28.5)	1379 (29.1)
Insulin	2860 (60.5)	2737 (57.8)
DPP-4 inhibitor	698 (14.8)	739 (15.6)
SGLT-2 inhibitor	310 (6.6)	265 (5.6)
Thiazolidinedione	92 (1.9)	102 (2.2)
Glinide	66 (1.4)	96 (2.0)
α-Glucosidase inhibitor	34 (0.7)	37 (0.8)

608

609 [#] Any of myocardial infarction, coronary artery bypass grafting, percutaneous coronary

610 intervention or ≥50% stenosis of coronary artery on angiography

611 Plus-minus values are means ± SD

612 ACE denotes angiotensin-converting enzyme

613 SGLT-2 denotes sodium-glucose cotransporter 2

614 DPP-4 denotes dipeptidyl peptidase 4

615 **Table 2. Primary and Secondary Cardiovascular Outcomes***

616

Outcome	**Albiglutide (N=4731)**	**Incidence Rate**	**Placebo (N=4732)**	**Incidence Rate**	**Hazard Ratio (95% CI)**	**P Value** ***Noninferiority*** ***Superiority***
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Primary composite outcome†	338 (7.1)	4.57	428 (9.0)	5.87	0.78 (0.68 – 0.90)	<0.0001 =0.0006
Secondary outcomes						***Superiority (nominal)***
Expanded composite††	373 (7.9)	5.06	468 (9.9)	6.45	0.78 (0.69 – 0.90)	<0.001
Death from cardiovascular causes	122 (2.6)	1.61	130 (2.7)	1.72	0.93 (0.73 – 1.19)	0.578
Fatal or nonfatal myocardial infarction	181 (3.8)	2.43	240 (5.1)	3.26	0.75 (0.61 – 0.90)	0.003
Fatal or nonfatal stroke	94 (2.0)	1.25	108 (2.3)	1.45	0.86	0.300

					(0.66 – 1.14)	
Death from cardiovascular causes or hospitalisation for heart failure	188 (4.0)	2.49	218 (4.6)	2.92	0.85 (0.70 – 1.04)	0.113
Death from any cause	196 (4.1)	2.44	205 (4.3)	2.56	0.95 (0.79 – 1.16)	0.644

* Hazard ratios and P vales were estimated using a Cox proportional-hazards model with treatment as the sole explanatory variable

† The primary composite outcome in the time-to-event analysis consisted of the first occurrence of death from cardiovascular causes (102 patients in the albiglutide group vs. 109 in the placebo group), nonfatal myocardial infarction (160 vs. 228) or nonfatal stroke (76 vs. 91). The P value is for superiority.

†† The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke or urgent coronary revascularization for unstable angina.

Table 3. Prespecified Adverse Events of Special Interest.[+]

	Albiglutide (n=4717)*	Placebo (n=4715)*	
	n (%)	n (%)	RR (95% CI)
Severe hypoglycemia	31 (0.7)	55 (1.2)	0.56 (0.36-0.87)
Pancreatitis†	10 (0.2)	7 (0.1)	1.43 (0.54-3.75)
Injection site reactions	86 (1.8)	29 (0.6)	2.96 (1.95-4.51)
Thyroid cancer	0 (0)	0 (0)	-
Hematologic neoplasia	9 (0.2)	5 (0.1)	1.80 (0.60-5.36)
Pancreatic cancer	6 (0.1)	5 (0.1)	1.20 (0.37-3.93)
Hypersensitivity Syndrome/Symptoms	45 (1.0)	48 (1.0)	0.94 (0.63-1.40)
Hepatobiliary disorders	51 (1.1)	41 (0.9)	1.24 (0.83-1.87)
Alanine aminotransferase ≥3xULN ‡	17 (0.4)	30 (0.6)	0.57 (0.31-1.03)
Alanine aminotransferase ≥5x ULN ‡	6 (0.1)	17 (0.4)	0.35 (0.14-0.89)
Bilirubin ≥2x ULN ‡	12 (0.3)	7 (0.1)	1.71 (0.68-4.35)
Serious gastrointestinal events	92 (2.0)	87 (1.8)	1.06 (0.79-1.41)
Appendicitis	3 (<0.1)	8 (0.2)	0.37 (0.10-1.41)
Atrial fibrillation/flutter	108 (2.3)	131 (2.8)	0.82 (0.64-1.06)
Pneumonia	131 (2.8)	138 (2.9)	0.95 (0.75-1.20)
Renal Impairment**	279 (5.9)	319 (6.8)	0.87 (0.75-1.02)
Diabetic retinopathy	78 (1.7)	89 (1.9)	0.88 (0.65-1.18)

[+]Definitions/details in Supplementary Appendix *In patients who took at least one dose.
RR=relative risk
† Events prospectively adjudicated to be definite or possible pancreatitis by treatment-blind adjudication committee
‡ ULN = Upper limit of normal. Hepatic enzyme elevation was pre-defined as an Adverse Event of Special Interest. There were 4 cases where the alanine aminotransferase ≥3xULN and bilirubin ≥2x ULN: 1 in the albiglutide group, 3 in the placebo group.
** Acute kidney injury was reported by investigators in 70 patients in the albiglutide group and in 80 in the placebo group.