

## Effect of the dual peroxisome proliferator-activated receptor- $\alpha/\gamma$ agonist aloglitazar on risk of cardiovascular disease in patients with type 2 diabetes (SYNCHRONY): a phase II, randomised, dose-ranging study

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### Summary

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**Background** Despite previous reports of potential adverse cardiovascular effects of peroxisome proliferator-activated receptor (PPAR) agonists, the promise for PPAR agonists to positively affect risk of cardiovascular disease in patients with type 2 diabetes is of continued interest. The SYNCHRONY study aimed to establish the glucose-lowering and lipid-modifying effects, and safety profile, of the dual PPAR- $\alpha$  and PPAR- $\gamma$  agonist aloglitazar.

**Methods** In this double-blind study, patients with type 2 diabetes (either drug-naive or pre-treated with  $\leq$ two oral agents) were enrolled from 47 sites in seven countries. After a single-blind, 4–5-week placebo run-in period, 332 patients were randomised double-blind (via an interactive voice-response system) to 16 weeks' treatment with aloglitazar at once-daily doses of 50  $\mu$ g, 150  $\mu$ g, 300  $\mu$ g, or 600  $\mu$ g, or matching placebo (n=55 in each group), or to open-label pioglitazone 45 mg once daily (n=57) as a reference. The primary efficacy endpoint was the change in glycosylated haemoglobin (HbA<sub>1c</sub>) concentration from baseline to the end of treatment. Patients who received at least one dose of study drug and had at least one evaluable post-baseline HbA<sub>1c</sub> measurement were included in the efficacy analysis. This study is registered with ClinicalTrials.gov, number NCT00388518.

**Findings** The efficacy analysis excluded six patients (n=0 in pioglitazone group; n=1 in each of placebo, 50  $\mu$ g, 150  $\mu$ g, and 600  $\mu$ g aloglitazar groups; and n=2 in 300  $\mu$ g aloglitazar group). Aloglitazar significantly reduced baseline HbA<sub>1c</sub> versus placebo in a dose-dependent manner, from  $-0.36\%$  (95% CI 0.00 to  $-0.70$ , p=0.048) with 50  $\mu$ g to  $-1.35\%$  ( $-0.99$  to  $-1.70$ , p<0.0001) with 600  $\mu$ g. The trend of changes over time suggests that the maximum effect of aloglitazar on HbA<sub>1c</sub> concentration was not yet reached after 16 weeks of treatment. Oedema, haemodilution, and weight gain occurred in a dose-dependent manner. However, at aloglitazar doses less than 300  $\mu$ g, no patients had congestive heart failure, frequency of oedema was similar to placebo (one case at 50  $\mu$ g, two at 150  $\mu$ g, and three with placebo) and less than with pioglitazone (four cases), and bodyweight gain was less than with pioglitazone (0.52 kg at 150  $\mu$ g vs 1.06 kg).

**Interpretation** The favourable balance in the safety and efficacy profile of aloglitazar represents encouraging short-term clinical data for this agent and provides good evidence to enter phase III investigation.

**Funding** F Hoffmann-La Roche AG (Switzerland).

### Introduction

Cardiovascular disease is the leading cause of death in individuals with type 2 diabetes, accounting for 50% of all deaths.<sup>1</sup> Clinical guidelines state that cardiovascular risk in patients with diabetes can be reduced by controlling dyslipidaemia, blood pressure, bodyweight, and hyperglycaemia,<sup>2,3</sup> but most patients still do not achieve recommended goals for these risk factors.<sup>2,4</sup>

Investigation of two intensive glycaemic control strategies in the Action to Control Cardiovascular Risk in Diabetes (ACCORD)<sup>5</sup> and Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE)<sup>6</sup> clinical trials in patients with type 2 diabetes at high risk of cardiovascular events confirmed the improvement of microvascular parameters associated with intensive glycaemic control. However, cardiovascular risk was not reduced in patients

who received intensive therapy for glycaemic control compared with those who received standard therapy. Despite not achieving the same amount of glycaemic control as in the ACCORD and ADVANCE trials, intensive glucose control in the Veterans Affairs Diabetes Trial (VADT) also did not show any benefit over standard therapy for major cardiovascular events in patients with poorly controlled type 2 diabetes.<sup>7</sup> These data suggest that a multifactorial intervention might be most appropriate for optimum reduction of cardiovascular risk.<sup>8</sup>

The potential for agonists of peroxisome proliferator-activated receptors (PPARs) to positively affect cardiovascular disease risk in patients with type 2 diabetes is of continued interest. The fibrates are agonists of PPAR- $\alpha$ , and their use in patients with type 2 diabetes can lead to improvements in lipid profiles.<sup>2</sup> The PPAR- $\gamma$  agonists pioglitazone and rosiglitazone are approved for glycaemic

control in type 2 diabetes. Pioglitazone therapy has been associated with reduced risk of negative cardiovascular outcomes in type 2 diabetes,<sup>9</sup> although the Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive) did not achieve the primary endpoint.<sup>10</sup> However, increasing safety concerns with the thiazolidinediones with regard to fluid retention, weight gain, and particularly congestive heart failure,<sup>9,11-17</sup> have resulted in the implementation of new label warnings for the use of these agents.<sup>18,19</sup> Clearly, an optimum PPAR agent with an improved safety profile that provides both effective glycaemic control and an improved lipid profile is needed. Compounds that affect both PPAR- $\alpha$  and PPAR- $\gamma$ , particularly with an optimised balance of agonist activity, might prove especially beneficial for patients with diabetes.

Several dual PPAR- $\alpha/\gamma$  agonists have been clinically developed; however, the emergence of several different types of toxic effects in clinical trials has resulted in their failure to progress beyond phase III development. Nonetheless, no consistent safety signal has been detected, probably because PPAR- $\alpha$  and PPAR- $\gamma$  each control the expression of many proteins that are involved in a range of biological processes. For example, development of tesaglitazar was discontinued because of indications that it could cause renal impairment, muraglitazar was linked with cardiovascular safety issues,<sup>20</sup> and earlier agents failed because of liver toxicity and tumours in rodents.

Aleglitazar is a new, balanced dual PPAR- $\alpha/\gamma$  agonist designed to optimise glycaemic and lipid benefits, and minimise PPAR-related adverse effects, weight gain, and peripheral oedema in the treatment of patients with type 2 diabetes. Binding and transactivation assays have suggested that aleglitazar is a potent and high-affinity ligand for both PPAR- $\alpha$  and PPAR- $\gamma$ .<sup>21</sup> This finding could distinguish aleglitazar from muraglitazar, which might have a higher affinity towards PPAR- $\gamma$ , and tesaglitazar, which might have a higher affinity towards PPAR- $\alpha$ .<sup>22</sup> Preclinical and phase I studies have shown favourable effects of aleglitazar on glycaemic control, insulin sensitivity, and dyslipidaemia.<sup>21</sup> The overall toxicity profile from non-clinical safety studies with aleglitazar was consistent with that of pioglitazone; the most relevant findings were reversible and showed an adequate safety margin.

The SYNCHRONY study was designed to establish the therapeutic dose of aleglitazar that would be most efficacious in terms of glucose and lipid control yet provide a favourable safety and tolerability profile in patients with type 2 diabetes.

## Methods

### Study design

The SYNCHRONY study was a randomised, double-blind, placebo-controlled, interventional, phase II, dose-ranging study undertaken at 47 sites in seven countries or regions

(Hong Kong, Italy, Mexico, Romania, Russian Federation, Serbia, and the USA). The study consisted of a single-blind, 4–5-week placebo run-in period to wash out previous antihyperglycaemic or weight-lowering drugs; a double-blind treatment period for 16 weeks (with open-label pioglitazone [Takeda Pharmaceutical Company, Osaka, Japan] as an active comparator); and a follow-up visit for safety assessment 4 weeks after the last treatment.

### Study population

Patients were recruited between Nov 21, 2006, and July 27, 2007, from hospital clinics and practising physicians specialised in the treatment of patients with diabetes. Patients had to meet all the following criteria for inclusion in this trial: age 18–75 years; diagnosis of type 2 diabetes; oral antidiabetic-naïve or previous treatment with a maximum of two antidiabetic agents (none at maximum dose); haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) 10·0% or less at screening and 7·0–10·0% at pre-randomisation visit; and fasting plasma glucose greater than 7·0 mmol/L at screening and 13·3 mmol/L or less at pre-randomisation visit.

Patients were excluded if they were diagnosed with type 1 diabetes, had impaired liver (alanine aminotransaminase or aspartate aminotransaminase greater than 2·5 times the upper limit of normal) or renal function (serum creatinine  $\geq$ 177  $\mu$ mol/L), anaemia (haemoglobin <110 g/L for men and <100 g/L for women), or uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg) at screening. Patients could not have had a myocardial infarction or stroke within 6 months of screening, congestive heart failure New York Heart Association (NYHA) class III or IV, or any serious illness at screening. Oral antidiabetic drugs and weight-lowering therapies were discontinued at the start of the placebo run-in period; patients treated with lipoprotein-modifying therapies (ie, fibrates) within 1 month before screening, apart from stable (1 month or longer) statin therapy, were excluded. All patients provided written informed consent, and the protocol was approved by applicable independent review committees or institutional review boards.

### Procedures

At study initiation, a diet and exercise plan to try to control bodyweight was discussed and implemented on the basis of the investigator's recommendation, and reinforced at all subsequent visits. All patients received two placebo capsules matched to aleglitazar during the single-blind placebo run-in period to keep study effects to a minimum and to check compliance before randomisation.

After the placebo run-in period, patients were randomly assigned to double-blind treatment with one of four doses of aleglitazar (50  $\mu$ g, 150  $\mu$ g, 300  $\mu$ g, or 600  $\mu$ g; F Hoffmann-La Roche AG, Basel, Switzerland) or matching placebo, each of which was given as a combination of two aleglitazar or placebo-matched capsules, or to open-label

45 mg pioglitazone. Patients, study site personnel, and sponsor were all blinded to treatment assignment. Dose selection was made on the basis of data from a 6-week phase I multiple-ascending dose study in patients with type 2 diabetes which suggested that 50 µg of aleglitazar might be the minimum and 600 µg the maximum effective daily dose with an acceptable tolerability profile (data on file, F Hoffmann-La Roche AG, Basel, Switzerland). All doses were administered orally once daily in the morning (irrespective of the time of breakfast) for the duration of the treatment period.

Randomisation was achieved via a central telephone (interactive voice-response system) with a stratified randomisation procedure to avoid an imbalance in diabetes severity ( $HbA_{1c} < 8.5\%$  and  $HbA_{1c} \geq 8.5\%$ ) across the treatment groups. Patient randomisation numbers were generated by the sponsor and incorporated into the double-blind or open-label labelling.

Three patient visits were scheduled during the placebo run-in period, at which we assessed fasting plasma

glucose. At week 2 of the run-in period, we assessed patients for safety, and a pre-randomisation visit was undertaken at day 23 or later to establish whether or not the patient met the final inclusion or exclusion criteria. During the 16-week treatment period, patients visited the clinic at baseline and weeks 2, 4, 8, 12, and 16, at which fasting blood samples were taken for assessment of glycaemic control, lipids, clinical chemistry, and pre-dose pharmacokinetics. All laboratory analyses were done by a central laboratory (Covance Central Laboratory Services, Indianapolis, USA; Geneva, Switzerland; and Singapore). Study drug was dispensed at baseline and at weeks 4, 8, and 12, and compliance was verified by used and unused drug supply that was returned at every dispensing visit.

We measured vital signs, physical examination (with check for peripheral oedema and cardiovascular events), bodyweight, and safety laboratory assessments at every clinic visit. Renal function was assessed with measurements of serum creatinine and estimated glomerular filtration rate (eGFR) with the modification of diet in renal disease

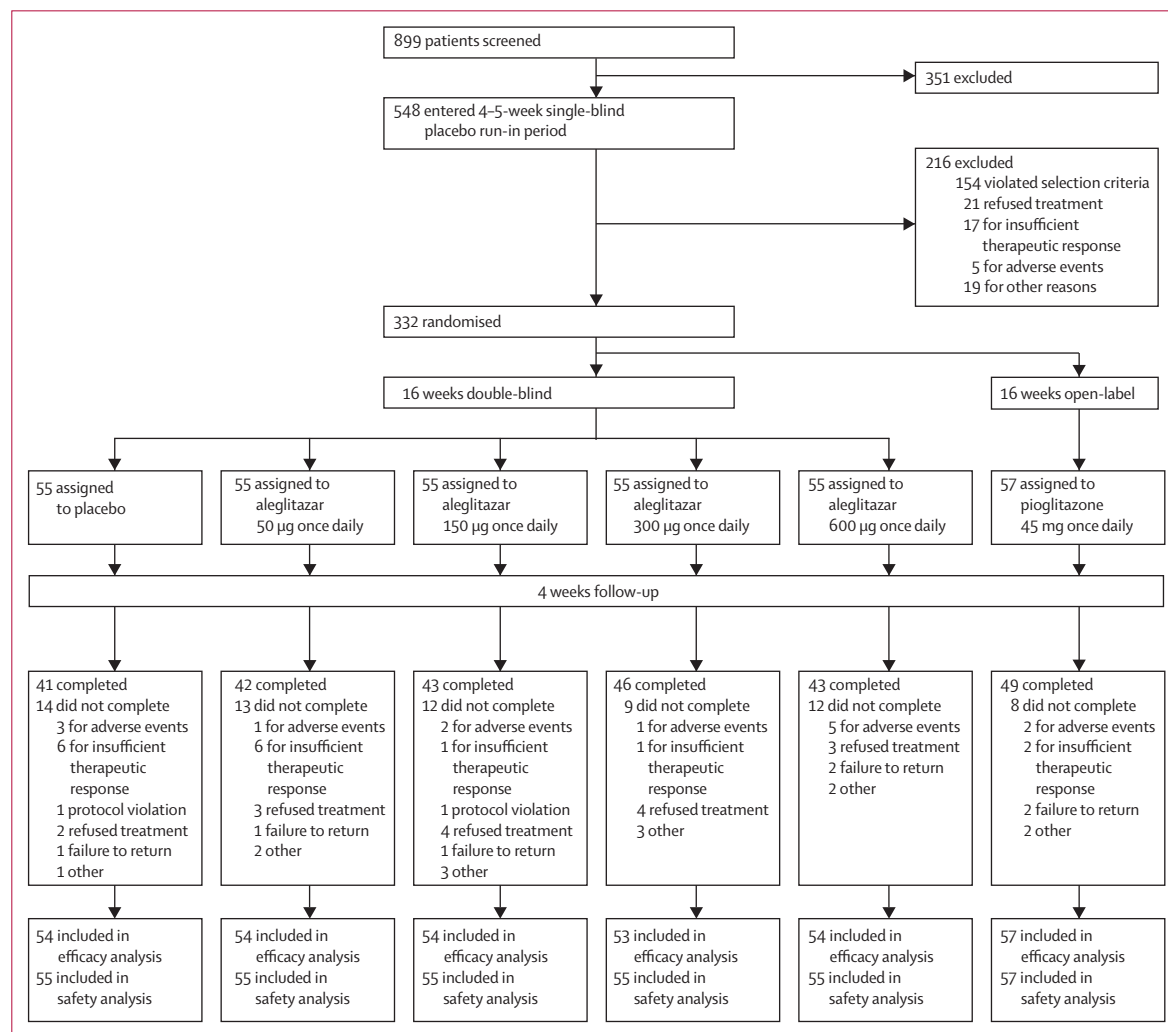


Figure 1: Trial profile

	Placebo (n=55)	Aleglitazar			Pioglitazone 45 mg (n=57)	
		50 µg (n=55)	150 µg (n=55)	300 µg (n=55)	600 µg (n=55)	
<b>Patient characteristics</b>						
Age (years)	56.5 (8.9)	55.7 (8.9)	55.2 (9.7)	52.6 (11.0)	56.9 (8.9)	54.4 (8.8)
Women	32 (58%)	31 (56%)	35 (64%)	27 (49%)	32 (58%)	33 (58%)
Body-mass index (kg/m <sup>2</sup> )	32.5 (7.5)	30.1 (6.6)	31.4 (7.3)	31.3 (6.6)	31.6 (7.0)	30.8 (5.5)
Diabetes duration (years)	2.9 (0.1–24.2)	4.6 (0.1–23.5)	3.6 (0.1–23.7)	2.3 (0.1–19.8)	2.6 (0.1–38.3)	2.7 (0.1–20.0)
Systolic blood pressure (mm Hg)	128.55 (13.8)	129.9 (15.1)	129.7 (13.3)	129.85 (13.8)	129.18 (15.2)	130.9 (13.4)
Diastolic blood pressure (mm Hg)	78.5 (7.1)	77.8 (8.5)	77.9 (9.5)	79.9 (8.9)	78.5 (10.3)	77.9 (7.2)
Hypertension	31 (56%)	37 (67%)	34 (62%)	25 (45%)	35 (64%)	34 (60%)
Current smoker	7 (13%)	8 (15%)	8 (15%)	11 (20%)	5 (9%)	9 (16%)
Heart failure (NYHA class I or II)	1 (2%)	2 (4%)	3 (6%)	2 (4%)	3 (6%)	2 (4%)
<b>Laboratory data</b>						
Haemoglobin A <sub>1c</sub> (%)	8.06% (0.75)	8.01% (0.76)	8.03% (0.75)	7.95% (0.77)	7.90% (0.64)	8.03% (0.80)
Fasting plasma glucose (mmol/L)	9.80 (2.53)	10.04 (2.17)	10.21 (2.08)	9.59 (2.35)	9.46 (1.87)	10.19 (1.89)
Triglycerides (mmol/L)	1.77 (0.80–14.61)	1.77 (0.80–9.95)	1.78 (0.56–8.58)	1.61 (0.64–5.68)	1.77 (0.77–7.11)	2.13 (0.69–18.36)
HDL cholesterol (mmol/L)	1.16 (0.26)	1.16 (0.26)	1.21 (0.37)	1.22 (0.33)	1.18 (0.27)	1.21 (0.33)
LDL cholesterol (mmol/L)	3.37 (1.00)	3.14 (1.01)	3.33 (0.84)	3.27 (1.04)	3.40 (0.89)	3.49 (1.03)
<b>Baseline medication use</b>						
Diabetes treatments						
Drug-naive	15 (27%)	11 (20%)	15 (27%)	15 (27%)	15 (27%)	14 (25%)
Monotherapy	25 (45%)	29 (53%)	26 (47%)	28 (51%)	31 (56%)	23 (40%)
Combination therapy	15 (27%)	15 (27%)	14 (25%)	12 (22%)	9 (16%)	20 (35%)
Antihypertensive therapy						
Diuretics	9 (16%)	11 (20%)	10 (18%)	5 (9%)	12 (22%)	7 (12%)
Angiotensin-converting enzyme inhibitors	18 (33%)	24 (44%)	20 (36%)	18 (33%)	18 (33%)	20 (35%)
Angiotensin II receptor antagonists	2 (4%)	3 (5%)	3 (5%)	1 (2%)	5 (9%)	3 (5%)
Statins*	10 (18%)	8 (15%)	7 (13%)	8 (15%)	9 (16%)	7 (12%)
Aspirin	9 (16%)	3 (5%)	8 (15%)	8 (15%)	8 (15%)	12 (21%)

Data are mean (SD), number (%), or median (range). NYHA=New York Heart Association. \*Patients were allowed to receive statin therapy during the trial if the dose had been stable for at least 1 month.

**Table 1: Baseline (after placebo run-in period) demographic and clinical characteristics (safety population)**

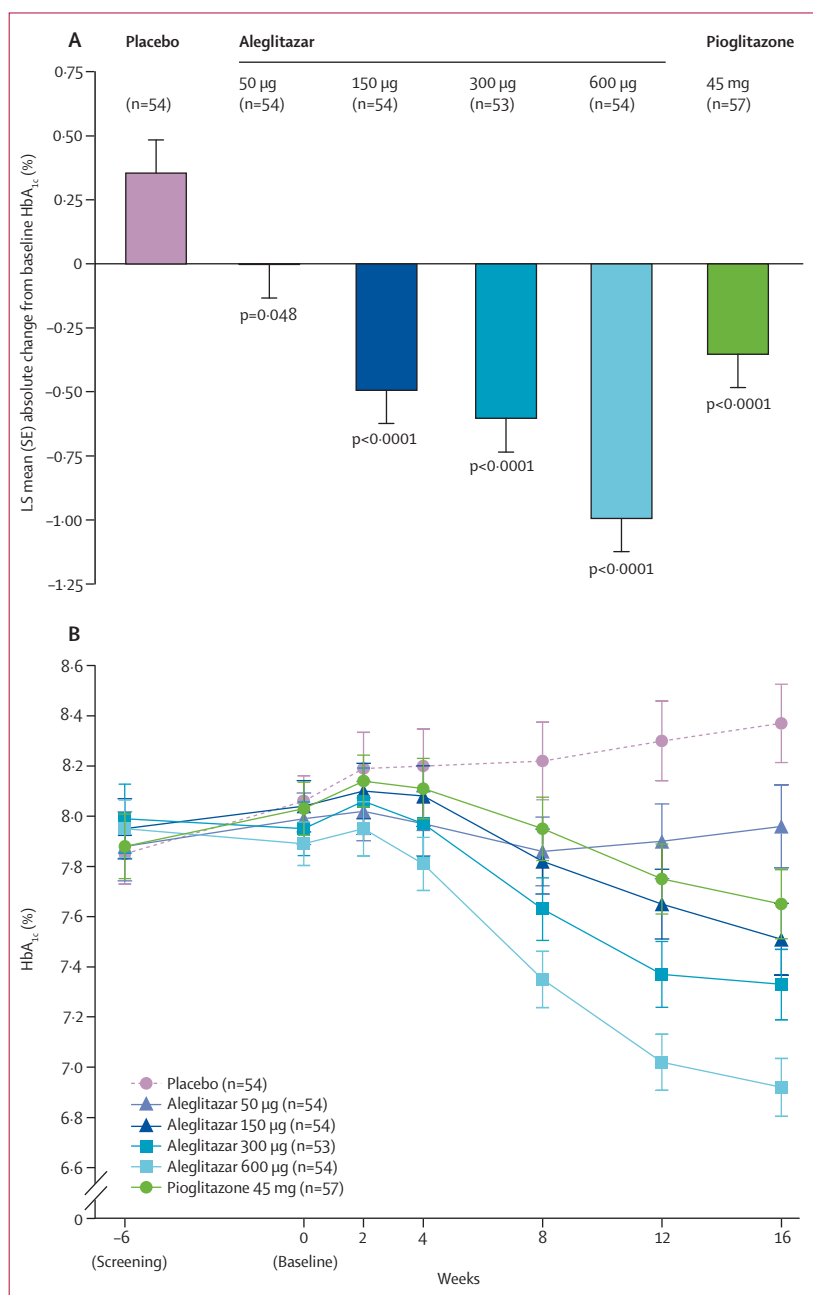
equation.<sup>23</sup> In addition to scheduled electrocardiograph at baseline and weeks 4, 8, and 16, and echocardiography at baseline and week 16, echocardiography was expeditiously done when moderate or severe oedema (defined as above two-thirds tibia to knee or above the knee) was observed at any point during the study. Suspected or diagnosed cardiovascular events (death [cardiovascular vs non-cardiovascular], heart failure, myocardial infarction, coronary revascularisation procedure, and admission to hospital for unstable angina) were reviewed and adjudicated according to prespecified endpoint definitions by an independent clinical events committee.

The primary objective of the study was to establish the doses of aleglitazar that were safe, well tolerated, and efficacious in improvement of glycaemic control in patients with type 2 diabetes. The primary endpoint for efficacy was absolute change in glycosylated haemoglobin (HbA<sub>1c</sub>) concentration from baseline to end of the treatment period. Secondary endpoints were changes from baseline in fasting plasma glucose and lipid profiles.

Safety analysis endpoints were peripheral oedema, cardiovascular events, bodyweight, and renal function.

### Statistical analysis

A minimum of 50 patients per treatment group were needed to ensure 80% power to detect a treatment difference of at least  $-0.82\%$  (each aleglitazar dose regimen vs placebo) for HbA<sub>1c</sub> change from baseline to the end of the treatment period, assuming common standard deviation of 1.45%, at a one-sided significance level of 0.025. This primary endpoint was assessed with ANCOVA to determine the least squares means of change from baseline and 95% CIs. The ANCOVA model included treatment and region as fixed effects and baseline HbA<sub>1c</sub> as the covariate. A pair-wise comparison of each aleglitazar dose regimen against placebo was done with a hierarchical decision procedure starting with the highest dose of aleglitazar. Comparisons of each aleglitazar dose regimen versus placebo were done at a two-sided significant level of 0.05. Comparisons between



**Figure 2: Effect on haemoglobin A<sub>1c</sub> concentration**  
 (A) Absolute change from baseline to end of treatment period (week 16) and (B) over time. Analysis undertaken in the intention-to-treat population, LOCF. p values are versus placebo. LS=least squares. HbA<sub>1c</sub>=haemoglobin A<sub>1c</sub>.

each aleglitazar dose regimen and the active comparator (pioglitazone) were descriptive in nature. Similar ANCOVA models were used to measure least squares means of change or percentage change from baseline and confidence intervals for secondary efficacy endpoints. For these secondary endpoints, the hierarchical decision procedure was not incorporated into the analysis. All patients who received at least one dose of randomised study drug and who had an evaluable baseline and at

least one evaluable post-baseline HbA<sub>1c</sub> measurement were included in the primary efficacy analysis. All patients who received at least one dose of randomised study drug were included in the safety analysis.

This study is registered with ClinicalTrials.gov, number NCT00388518.

**Role of the funding source**

In collaboration with the investigators, the sponsor of the trial contributed to the design of the study, collection of data, statistical analysis, and interpretation and reporting of the results. As defined by the protocol, all cardiovascular events were assessed by an independent adjudication committee. Data were recorded at participating clinical centres and maintained by the sponsor. The report was prepared by the authors, with contributions from the sponsor. The authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

Figure 1 shows the trial profile. 332 patients (Hong Kong 33, Italy 19, Mexico 101, Romania 39, Russian Federation 54, Serbia 30, USA 56) were enrolled and randomly assigned to a study group (figure 1). Demographic characteristics and baseline disease characteristics were well balanced between treatment groups (table 1). About half of all patients had received previous monotherapy treatment for diabetes, with similar numbers of the remaining patients controlled with diet alone or with a combination of oral antidiabetic drugs. At the start of the double-blind treatment period, roughly half of all patients were taking prescribed anti-hypertensive medications, and statin use was recorded in 15% of patients (table 1).

Aleglitazar significantly decreased HbA<sub>1c</sub> from baseline after 16 weeks of treatment in a dose-dependent manner (figure 2A). The trend of changes over time could suggest that the maximum effect of aleglitazar on HbA<sub>1c</sub> concentration was not yet reached after 16 weeks of treatment (figure 2B). We recorded a similar dose-response for fasting plasma glucose (figure 3). The time course suggests that fasting plasma glucose was already decreased at the first visit after randomisation (2 weeks) and that the maximum effect occurred after 8 weeks.

Although the study was not powered to assess significant differences between aleglitazar and pioglitazone, the 150 µg dose of aleglitazar was associated with a similar reduction versus placebo in both HbA<sub>1c</sub> (-0.85%, 95% CI -0.50 to -1.20, p<0.0001) and concentrations of fasting plasma glucose (-2.16 mmol/L, -1.35 to -2.98, p<0.0001) to that detected with 45 mg pioglitazone (-0.71%, -0.36 to -1.06, p<0.0001; and -2.10 mmol/L, -1.29 to -2.90, p<0.0001, respectively).

Treatment for 16 weeks with aleglitazar resulted in dose-dependent improvements in lipid parameters. We documented significant decreases in triglycerides (p<0.001

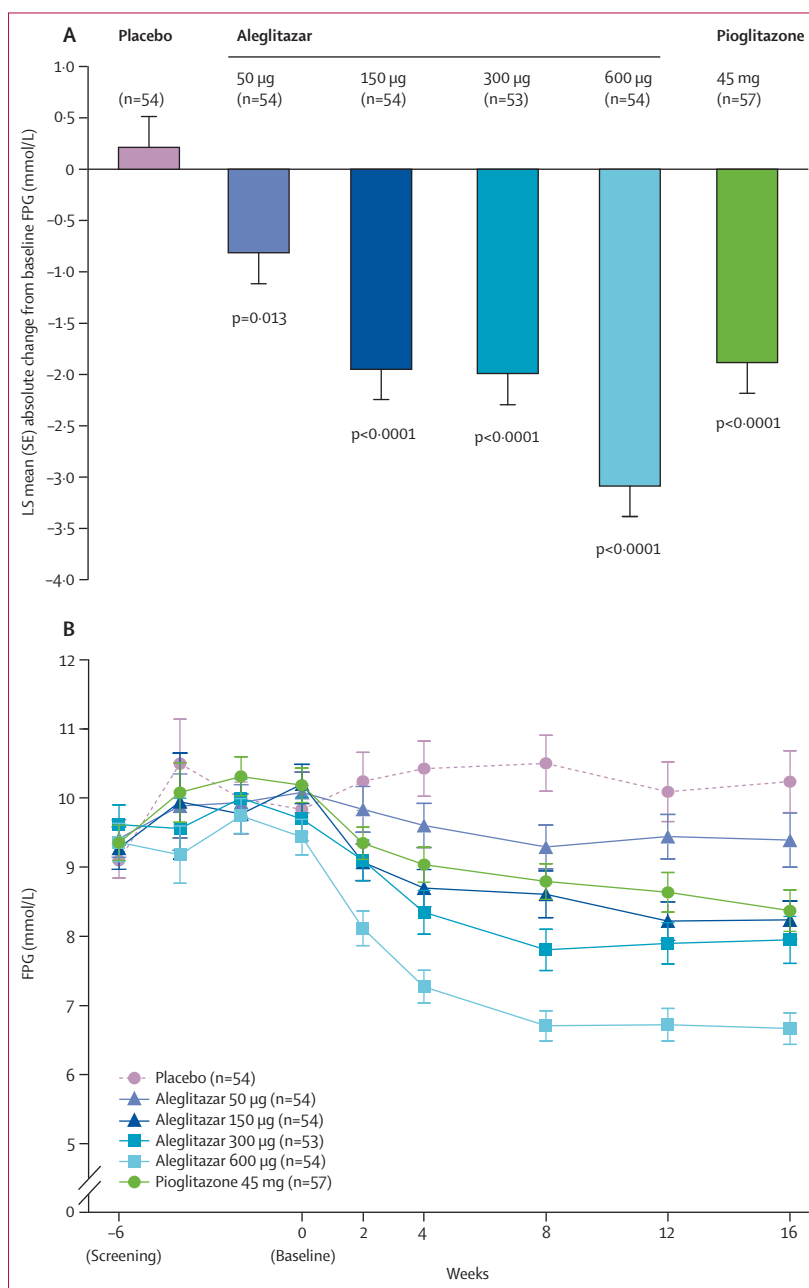
for percentage changes; figure 4A) and HDL cholesterol ( $p < 0.05$  for percentage changes; figure 4B) compared with placebo at all doses of aleglitazar. We recorded significant reductions in LDL cholesterol at doses of 150  $\mu\text{g}$  or higher compared with placebo ( $p < 0.05$  for percentage changes; figure 4C). The maximum effect on lipid parameters seemed to be reached after 8 weeks of treatment for HDL cholesterol and after 4 weeks of treatment for LDL cholesterol and triglycerides (data not shown). Apolipoprotein B concentrations were significantly reduced after treatment with all doses of aleglitazar compared with placebo ( $p < 0.001$ ; figure 4D). With the 150  $\mu\text{g}$  dose of aleglitazar, the maximum effect was approached for triglycerides (placebo-adjusted reduction  $-43.4\%$ , 95% CI  $-27.4$  to  $-59.4$ ) and HDL cholesterol ( $20.7\%$ , 13.2–28.2). Placebo-adjusted reduction in LDL cholesterol with the 150  $\mu\text{g}$  dose of aleglitazar was  $-15.5\%$  (95% CI  $-5.4$  to  $-25.6$ ). Treatment with 150  $\mu\text{g}$  aleglitazar also produced a greater effect on triglycerides, HDL cholesterol, and LDL cholesterol than did 45 mg pioglitazone (figure 4).

Systolic and diastolic blood pressure measurements were slightly reduced after treatment with aleglitazar. Changes in systolic blood pressure ranged from  $-3.1$  mm Hg (SE 1.4) for the 50  $\mu\text{g}$  group to  $-7.4$  mm Hg (1.4) for the 300  $\mu\text{g}$  group, versus  $-2.6$  mm Hg (1.4) with placebo. Changes in diastolic blood pressure ranged from  $-1.7$  mm Hg (1.0) for the 50  $\mu\text{g}$  group to  $-3.8$  mm Hg (1.0) for the 600  $\mu\text{g}$  group versus  $-0.9$  mm Hg (1.0) with placebo. Changes in the pioglitazone group were  $-5.7$  mm Hg (1.4) and  $-4.7$  mm Hg (1.0), respectively.

We noted reductions from baseline with aleglitazar for other biomarkers of cardiovascular risk, including high-sensitivity C-reactive protein (median reduction ranging from  $-0.14$  mg/L [range  $-21.70$  to  $38.17$ ] from a baseline of  $4.53$  mg/L with 50  $\mu\text{g}$  to  $-1.73$  mg/L [ $-49.4$  to  $5.92$ ] from a baseline of  $6.85$  mg/L with 600  $\mu\text{g}$ ); plasminogen-activator inhibitor-1 (mean reduction ranging from  $-5.0$  U/mL [SE 1.6] from a baseline of  $22.7$  U/mL with 150  $\mu\text{g}$  to  $-9.0$  U/mL [1.6] from a baseline of  $17.9$  U/mL with 600  $\mu\text{g}$ ); and fibrinogen (mean reduction ranging from  $-0.60$   $\mu\text{mol/L}$  [0.26] from a baseline of  $10.28$   $\mu\text{mol/L}$  with 50  $\mu\text{g}$  to  $-2.29$   $\mu\text{mol/L}$  [0.26] from a baseline of  $9.98$   $\mu\text{mol/L}$  with 600  $\mu\text{g}$ ).

All doses of aleglitazar were well tolerated throughout the study, with similar numbers of patients having adverse events in the aleglitazar treatment groups (21–26 of 55 patients per treatment group) and the placebo group (25/55), compared with the pioglitazone group (30/57). Most adverse events were considered unrelated to treatment, and most were of mild intensity. No patients died during the study.

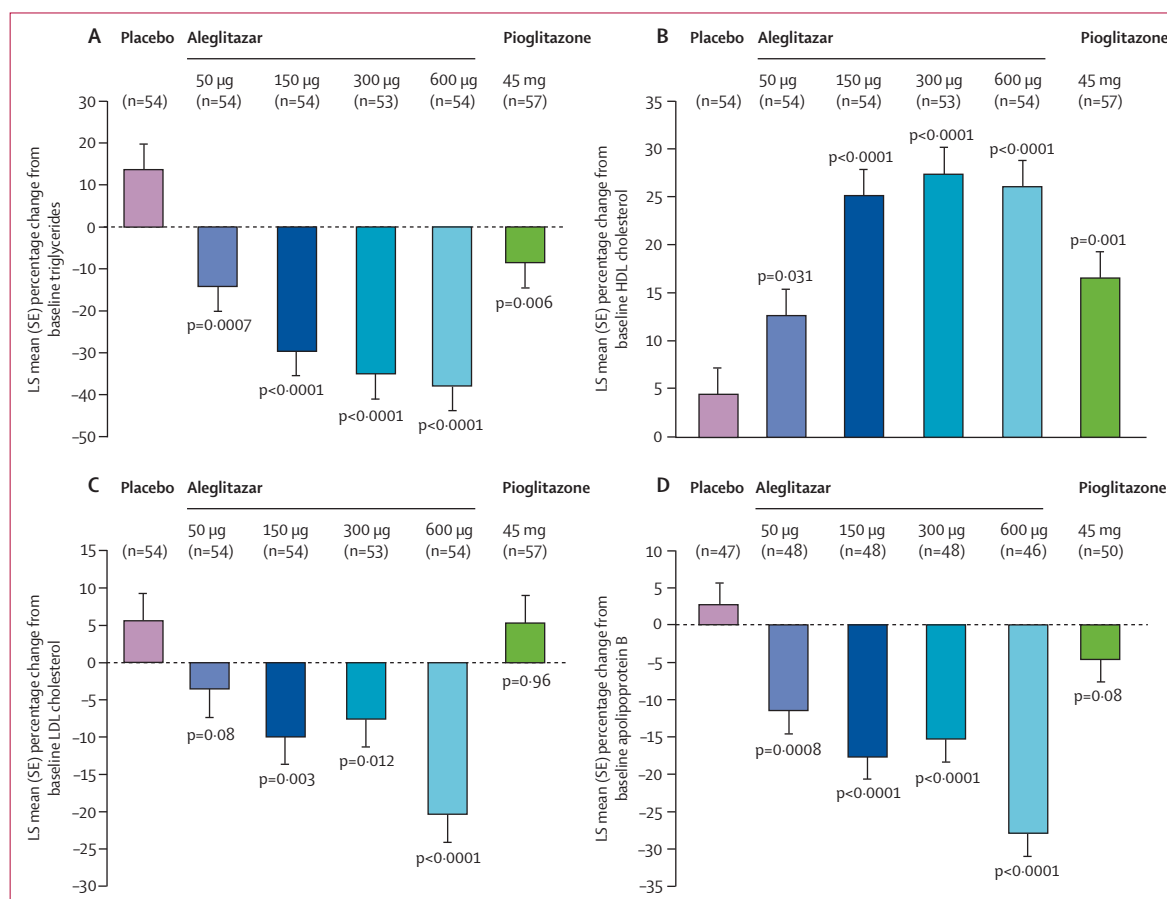
The most frequently reported adverse events (reported by three or more patients in any one treatment group) were peripheral oedema, nasopharyngitis, increased blood creatine phosphokinase (CPK), and upper respiratory tract infection (table 2). No patient in this study had severe oedema. The number of cases of



**Figure 3: Effect on fasting plasma glucose**

(A) Absolute change from baseline to end of treatment period (week 16) and (B) over time. Analysis undertaken in the intention-to-treat population, LOCF. p values are versus placebo. LS=least squares. FPG=fasting plasma glucose.

peripheral oedema was greatest with higher doses of aleglitazar ( $\geq 300$   $\mu\text{g}$ ) (table 2). CPK was measured at every clinic visit as part of the schedule of laboratory assessments. One patient in the 300  $\mu\text{g}$  group had CPK elevation of five times or higher than the upper limits of normal and one patient in the 600  $\mu\text{g}$  aleglitazar group ten times or higher than the upper limits of normal. CPK returned to baseline in both patients at the next clinic visit while remaining on study drug; although no muscle



**Figure 4: Effect on lipid parameters**  
 Percentage change from baseline lipid concentrations to end of treatment period (week 16) for (A) triglycerides, (B) HDL cholesterol, (C) LDL cholesterol, and (D) apolipoprotein B. Analysis undertaken in the intention-to-treat population, LOCF. p values are versus placebo. LS=least squares.

	Placebo (n=55)	Aleglitazar				Pioglitazone 45 mg (n=57)
		50 µg (n=55)	150 µg (n=55)	300 µg (n=55)	600 µg (n=55)	
Peripheral oedema	3 (5%)	1 (2%)	2 (4%)	6 (11%)	5 (9%)	4 (7%)
Nasopharyngitis	4 (7%)	1 (2%)	3 (5%)	1 (2%)	3 (5%)	3 (5%)
Increased blood creatine phosphokinase	3 (5%)	0	1 (2%)	3 (5%)	5 (9%)	2 (4%)
Upper respiratory tract infection	3 (5%)	2 (4%)	1 (2%)	4 (7%)	2 (4%)	0
Arthralgia	2 (4%)	0	3 (5%)	0	1 (2%)	1 (2%)
Influenza	0	0	0	1 (2%)	2 (4%)	3 (5%)
Decreased haemoglobin	1 (2%)	0	0	0	4 (7%)	0
Decreased white blood cell count	0	0	0	0	3 (5%)	0

Data are number (%) of patients with adverse event. Adverse events presented are those reported by three or more patients in any one treatment group.

**Table 2: Most frequently reported adverse events**

symptoms were noted for these patients, an explanation was provided for both (physical exercise and a fall). We recorded no clinically significant changes in electrocardiograph or echocardiography parameters after treatment with aleglitazar (data not shown).

Four patients had five serious adverse events (vasovagal syncope [150 µg aleglitazar], dyspepsia and intervertebral disc protrusion [300 µg aleglitazar], non-cardiac chest pain [600 µg aleglitazar], and abdominal hernia [pioglitazone]); however, none of the serious adverse events was considered related to study treatment. Between nine and 13 patients in individual aleglitazar groups withdrew from the study prematurely, compared with 14 placebo patients and eight patients in the pioglitazone group (figure 1). Five patients receiving the highest dose (600 µg) of aleglitazar were withdrawn as the result of an adverse event, compared with three in the placebo group and one or two patients in each of the other groups (figure 1).

Nine events triggered adjudication by the clinical events committee for cardiac safety. Positive adjudication for congestive heart failure occurred in two patients given aleglitazar (300 µg and 600 µg dose). No events of myocardial infarction or coronary revascularisation were diagnosed during the study.

We noted a dose-dependent increase from baseline in bodyweight over time for all doses of aleglitazar and for pioglitazone (table 3). The weight gain was numerically

less with aleglitazar doses up to 150 µg than with 45 mg pioglitazone. With higher doses of aleglitazar, however, weight gain was numerically greater than with 45 mg pioglitazone. We noted dose-dependent reductions in haemoglobin at all doses of aleglitazar and with pioglitazone (table 3). Reductions in haemoglobin were less with doses up to 150 µg of aleglitazar than with pioglitazone. Incidence of anaemia was as expected with this class of agent, and was mainly reported at higher doses (two cases with placebo, two at the 50 µg dose, none at the 150 µg dose, one at the 300 µg dose, nine at the 600 µg dose, and none with pioglitazone).

We recorded dose-related increases in serum creatinine after treatment with aleglitazar compared with placebo, with a corresponding decrease in eGFR (table 3). The increases in serum creatinine were mild with the lower doses (<10% increases at doses up to 150 µg aleglitazar). Maximum effects on renal function seemed to be reached after 4 weeks of treatment, with no increase thereafter (data not shown).

## Discussion

Aleglitazar treatment produced significant, dose-dependent improvements in HbA<sub>1c</sub> concentrations and fasting plasma glucose compared with placebo, and significant dose-dependent improvements in all lipid parameters, including LDL cholesterol. The 150 µg dose provided glycaemic effects similar to the 45 mg pioglitazone reference group. Effects on lipids were recorded early after week 0, and the 150 µg dose of aleglitazar approached a maximum treatment effect on triglycerides and HDL cholesterol. We also recorded a 10% reduction from baseline LDL cholesterol with the 150 µg dose of aleglitazar. For comparison, the available thiazolidinediones increase LDL cholesterol by 2–16% with pioglitazone<sup>24,25</sup> and by 12–23% with rosiglitazone.<sup>18,24</sup>

Importantly, aleglitazar seemed to be safe and well tolerated over the course of the 16-week study. The sample size of this study was too small to make definitive conclusions, but that no myocardial infarction or stroke events occurred is reassuring. By contrast, excess cardiovascular events have been noted for patients given muraglitazar and rosiglitazone after a fairly short exposure to treatment.<sup>11,20</sup>

Monitoring of bodyweight gain and peripheral oedema, both known effects for PPAR-γ activation, also suggested that these side-effects were less frequent with low doses of aleglitazar than with pioglitazone. We recorded dose-dependent increases in bodyweight changes with aleglitazar; such increases in bodyweight were less in the 150 µg aleglitazar group than in the pioglitazone group. The frequency of oedema in the 150 µg aleglitazar group was similar to placebo and numerically lower than with pioglitazone. Changes in serum creatinine and eGFR were dose-dependent; eGFR decreased by less than 10% in the 150 µg aleglitazar group, reaching a plateau after 4 weeks of treatment,

	Placebo	Aleglitazar				Pioglitazone 45 mg
		50 µg	150 µg	300 µg	600 µg	
<b>Bodyweight (kg)</b>						
Number of patients	54	54	54	53	54	57
LS mean baseline (SE)	86.7 (2.8)	81.3 (2.8)	82.1 (2.8)	88.0 (2.9)	83.3 (2.8)	82.5 (2.8)
LS mean absolute change from baseline (SE)	-0.85 (0.40)	-0.24 (0.40)	0.52 (0.39)	1.18 (0.40)	2.72 (0.39)	1.06 (0.40)
<b>Haemoglobin (g/L)</b>						
Number of patients	40	41	44	46	42	50
LS mean baseline (SE)	144.8 (1.7)	140.8 (1.7)	140.9 (1.7)	146.2 (1.7)	142.8 (1.7)	145.2 (1.7)
LS mean absolute difference from baseline (SE)	0.18 (1.38)	-2.20 (1.37)	-4.80 (1.32)	-8.83 (1.29)	-13.93 (1.35)	-6.12 (1.24)
<b>Serum creatinine (µmol/L)</b>						
Number of patients	41	42	45	47	45	50
LS mean baseline (SE)	73.6 (2.3)	72.7 (2.3)	69.1 (2.3)	71.7 (2.3)	74.2 (2.3)	70.6 (2.3)
LS mean percentage change from baseline (SE)	-0.32% (2.14)	4.84% (2.11)	7.16% (2.04)	13.24% (2.00)	15.70% (2.04)	3.18% (1.94)
<b>Estimated GFR (mL/min/1.73 m<sup>2</sup>)</b>						
Number of patients	41	42	45	47	45	50
LS mean baseline (SE)	86.4 (3.0)	87.6 (3.0)	93.7 (3.0)	92.6 (3.0)	82.5 (3.0)	89.1 (2.9)
LS mean percentage change from baseline (SE)	2.67% (2.10)	-3.91% (2.07)	-6.35% (2.00)	-11.5% (1.96)	-14.06% (2.00)	-1.35% (1.90)

Intention-to-treat population (LOCF) used for analysis of bodyweight. Safety population (observed) used for all other parameters. LS=least squares. GFR=glomerular filtration rate.

**Table 3: Bodyweight and laboratory variables**

with no change thereafter. The increase in serum creatinine might be a haemodynamic effect caused by PPAR activation. A study of renal function to further investigate the mechanism behind this effect, and its reversibility, is in progress.

Slowed progression of carotid intima media thickness and slowed progression of coronary atherosclerosis were reported in patients treated for 18 months with pioglitazone—a PPAR agonist associated with an improved lipid profile—compared with those given glimepiride.<sup>25,26</sup> In our open-label comparison, the extent of improvements in LDL cholesterol, HDL cholesterol, and triglycerides was numerically greater in the 150 µg aleglitazar group than in the pioglitazone group after 16 weeks. Although long-term improvements in lipid profiles have yet to be confirmed, the differences noted between these two compounds are substantial and could provide benefits for cardiovascular outcomes in patients with type 2 diabetes. However, further research is needed.

The broad range of lipid improvements associated with aleglitazar addresses the pattern of dyslipidaemia often noted in patients with type 2 diabetes, which includes high concentrations of triglycerides, low concentrations of HDL cholesterol, and moderate rises in LDL cholesterol,

with an increased concentration of small, dense, and potentially more atherogenic particles. Although raised LDL cholesterol is the most recognised primary target of lipid-lowering therapy in diabetes, correction of hypertriglyceridaemia and low concentrations of HDL cholesterol is recommended for patients with type 2 diabetes with or without significantly raised LDL cholesterol.<sup>2,27</sup>

The SYNCHRONY study was designed to recruit patients who would as closely as possible represent a typical population with type 2 diabetes. However, there are limitations to the generalisation of these data. Exclusion criteria led largely to the enrolment of patients who were not at particularly high risk of cardiovascular disease. Patients generally did not have a long-standing history of diabetes, although they had poor glycaemic control at screening and three-quarters of patients were taking antidiabetic medications at study entry. Since all oral antidiabetic drugs were washed out before randomisation, no information about the effects of aleglitazar in combination with these agents can be surmised. Clinical pharmacology studies have ruled out a pharmacokinetic interaction with statins (data on file, F Hoffmann-La Roche AG, Basel, Switzerland) and, despite the small sample sizes, subgroup analyses from the SYNCHRONY study showed no apparent difference in response in statin users (15% of the trial population) versus non-users (data not shown). Additionally, we recorded no differences for creatinine change in users versus non-users of angiotensin-converting enzyme inhibitors (data not shown). The 16-week course of therapy in the present trial can be regarded as standard duration for a phase II clinical trial. Although 16 weeks is too short to show long-term cardiovascular safety and tolerability of aleglitazar, the absence of any safety signals in the trial is encouraging for the use of the agent in long-term trials.

Apart from the pharmacodynamic effects in this phase II study, we cannot make any clinically applicable conclusion for long-term outcomes. However, the significant changes in lipids and glycaemic endpoints coupled with the favourable safety profile represent promising data for aleglitazar and provide good evidence to enter phase III clinical investigation. Recruitment of patients with acute coronary syndromes and type 2 diabetes into a large, long-term, phase III trial for the secondary prevention of cardiovascular morbidity and mortality will begin in February, 2010, to further establish the safety and efficacy of this promising new agent.

#### Contributors

RRH participated in the planning of the study, collection of the data, supervision of the analyses, interpretation of the results, and writing of the report. AML participated in the planning of the study and interpretation of the results. SM participated in the planning of the study, collection of the data, and interpretation of the results. MR participated in the planning of the study, analysis of the data, and interpretation of the results. CC participated in the planning of the study and interpretation of the results. MH participated in the planning of the study and interpretation of the results. RRH and MH wrote the first draft of the Article. All authors were involved in the planning of the Article, critical

review and editing of the first draft, and subsequent revisions to the report. Additional input was provided by internal Roche personnel.

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#### Conflicts of interest

RRH has served on advisory boards and has received consulting fees and research support from Hoffmann-La Roche. AML has received research support from Hoffmann-La Roche and Takeda Pharmaceuticals. SM has served on speaker bureaux for Takeda Pharmaceuticals and has received research support from GlaxoSmithKline and Sanofi-Aventis. MR is an employee of Hoffmann-La Roche. CC and MH are employees of and hold stock interest in F Hoffmann-La Roche AG.

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#### References

- WHO. Diabetes. Fact sheet No 312. Geneva: World Health Organization, 2008.
- American Diabetes Association. Standards of medical care in diabetes—2008. *Diabetes Care* 2008; **31** (suppl 1): S12–54.
- Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Eur Heart J* 2007; **28**: 2375–414.
- Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004; **291**: 335–42.
- Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545–59.
- Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560–72.
- Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**: 129–39.
- Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; **348**: 383–93.
- Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; **298**: 1180–88.
- Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366**: 1279–89.

- 11 Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**: 2457–71.
- 12 Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; **298**: 1189–95.
- 13 Erdmann E, Charbonnel B, Wilcox RG, et al. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care* 2007; **30**: 2773–78.
- 14 Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol* 2007; **49**: 1772–80.
- 15 Eurich DT, McAlister FA, Blackburn DF, et al. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. *BMJ* 2007; **335**: 497.
- 16 Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med* 2007; **357**: 28–38.
- 17 Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA* 2007; **298**: 2634–43.
- 18 Avandia (rosiglitazone maleate) Tablets. US Prescribing Information. Research Triangle Park: GlaxoSmithKline, 2008.
- 19 Actos (pioglitazone hydrochloride) Tablets. US Prescribing Information. Deerfield: Takeda Pharmaceuticals America, 2007.
- 20 Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005; **294**: 2581–86.
- 21 Bénardeau A, Benz J, Binggeli A, et al. Aleglitazar, a new, potent, and balanced dual PPAR $\alpha$ / $\gamma$  agonist for the treatment of type II diabetes. *Bioorg Med Chem Lett* 2009; **19**: 2468–73.
- 22 Balakumar P, Rose M, Ganti SS, Krishan P, Singh M. PPAR dual agonists: are they opening Pandora's Box? *Pharmacol Res* 2007; **56**: 91–98.
- 23 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130**: 461–70.
- 24 Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005; **28**: 1547–54.
- 25 Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA* 2008; **299**: 1561–73.
- 26 Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006; **296**: 2572–81.
- 27 Ryden L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007; **28**: 88–136.