# Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial

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## Summary

**Background** Dyslipidaemia remains a significant risk factor for cardiovascular disease and additional lipid-modifying treatments are warranted to further decrease the cardiovascular disease burden. We assessed the safety, tolerability and efficacy of a novel cholesterol esterase transfer protein (CETP) inhibitor TA-8995 in patients with mild dyslipidaemia.

**Methods** In this randomised, double-blind, placebo-controlled, parallel-group phase 2 trial, we recruited patients (aged 18–75 years) from 17 sites (hospitals and independent clinical research organisations) in the Netherlands and Denmark with fasting LDL cholesterol levels between 2·5 mmol/L and 4·5 mmol/L, HDL cholesterol levels between 0·8 and 1·8 mmol/L and triglyceride levels below 4·5 mmol/L after washout of lipid-lowering treatments. Patients were randomly allocated (1:1) by a computer-generated randomisation schedule to receive one of the following nine treatments: a once a day dose of 1 mg, 2·5 mg, 5 mg, or 10 mg TA-8995 or matching placebo; 10 mg TA-8995 plus 20 mg atorvastatin; 10 mg TA-8995 plus 10 mg rosuvastatin or 20 mg atorvastatin or 10 mg rosuvastatin alone. We overencapsulated statins to achieve masking. The primary outcome was percentage change in LDL cholesterol and HDL cholesterol from baseline at week 12, analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT01970215.

**Findings** Between Aug 15, 2013, and Jan 10, 2014, 364 patients were enrolled. At week 12, LDL cholesterol levels were reduced by 27·4% in patients assigned to the 1 mg dose, 32·7% in patients given the 2·5 mg dose, 45·3% in those given the 5 mg dose, and 45·3% in those given the 10 mg dose (p<0·0001). LDL cholesterol levels were reduced by 68·2% in patients given 10 mg TA-8995 plus atorvastatin, and by 63·3% in patients given rosuvastatin plus 10 mg TA-8995 (p<0·0001). A daily dose of 1 mg TA-8995 increased HDL cholesterol levels by 75·8%, 2·5 mg by 124·3%, 5 mg by 157·1%, and 10 mg dose by 179·0% (p<0·0001). In patients receiving 10 mg TA-8995 and 20 mg atorvastatin HDL cholesterol levels increased by 152·1% and in patients receiving 10 mg TA-8995 and 10 mg rosuvastatin by 157·5%. We recorded no serious adverse events or signs of liver or muscle toxic effects.

**Interpretation** TA-8995, a novel CETP inhibitor, is well tolerated and has beneficial effects on lipids and apolipoproteins in patients with mild dyslipidaemia. A cardiovascular disease outcome trial is needed to translate these effects into a reduction of cardiovascular disease events.

**Funding** Dezima.

## Introduction

Robust evidence exists showing that reducing the concentration of LDL cholesterol results in a significant reduction in the risk of having a major cardiovascular event.[1] For every 1·0 mmol/L reduction in LDL cholesterol, the risk of having a cardiovascular event falls by roughly 22%.[1] However, many people remain at an unacceptably high risk of having a future cardiovascular event despite treatment with optimum doses of effective statins and other lipid lowering treatments. Although the residual risk relates (at least partly) to factors other than plasma lipids, in many patients the concentration of LDL cholesterol remains high despite statin treatment. This finding has stimulated a major effort to develop drugs that provide additional lowering of LDL cholesterol when coadministered with a statin.

Several LDL cholesterol-lowering strategies are being investigated, and inhibitors of cholesteryl ester transfer protein (CETP), by virtue of their effect on the transfer of cholesterol into atherogenic LDL particles,[2] reduce LDL cholesterol levels.

Initial attempts to show cardioprotective effects of CETP inhibition with torcetrapib and dalcetrapib in human beings have failed.[3,4] Nevertheless, the hypothesis of a beneficial effect of CETP lowering is being tested in two large clinical outcome trials (REVEAL [NCT01252953] and ACCELERATE [NCT01687998]) in which investigators are studying CETP inhibitors that do not possess the adverse off-target effects of torcetrapib.

In a phase 1 study[5] in human beings, TA-8995, a novel inhibitor of CETP, exerted potent effects on both pro-atherogenic and anti-atherogenic lipoprotein particles, without the off-target effects of torcetrapib.

We aimed to assess the safety and efficacy of TA-8995 as monotherapy and combined with statins in patients with mild dyslipidaemia.

## Methods

### Study design and participants

In this randomised, double-blind, placebo-controlled, parallel-group phase 2 trial, we recruited men and women (aged 18–75 years) from 17 sites (hospitals and independent clinical research organisations) in the Netherlands and Denmark with fasting LDL cholesterol levels between 2·5 mmol/L and 4·5 mmol/L, HDL cholesterol levels between 0·8 mmol/L and 1·8 mmol/L and triglyceride levels below 4·5 mmol/L after run-in, or washout of previous lipid-lowering treatments. Key exclusion criteria included clinical manifestations of atherosclerotic vascular disease, type 1 diabetes, uncontrolled type 2 diabetes (haemoglobin $A_{1c}$ ≥8%), uncontrolled hypertension, history of hyperaldosteronism, active muscle disease or persistent creatine kinase more than three times the upper limit of normal, clinically significant renal or hepatic dysfunction, or evidence of any other clinically significant non-cardiac disease.

The study was in compliance with the ethical principles in the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice, and appropriate regulatory requirements. The protocol was reviewed and approved by the Institutional Review Board of each participating centre and each patient provided written informed consent.

### Randomisation and masking

We randomly assigned (1:1) patients to receive one of the following nine treatments: 1 mg, 2·5 mg, 5 mg, or 10 mg TA-8995 or matching placebo; 10 mg TA-8995 plus 20 mg atorvastatin, 10 mg TA-8995 plus 10 mg rosuvastatin, 20 mg atorvastatin, or 10 mg rosuvastatin. Patients were assigned to treatment regimens with a computer-generated randomisation schedule coordinated by a centralised computer system. Treatment allocation process was by minimisation. Trial treatments were supplied as TA-8995 capsules and matching placebos. Additionally, atorvastatin and rosuvastatin were overencapsulated and all patients whose treatment did not include a statin were also given a matching placebo-statin to maintain masking. During the trial, the patients and all trial-related personnel were masked to individual results of fasting lipid profile measurements, with the exception of safety alerts which were sent to an independent safety group handling all safety-related issues during the trial.

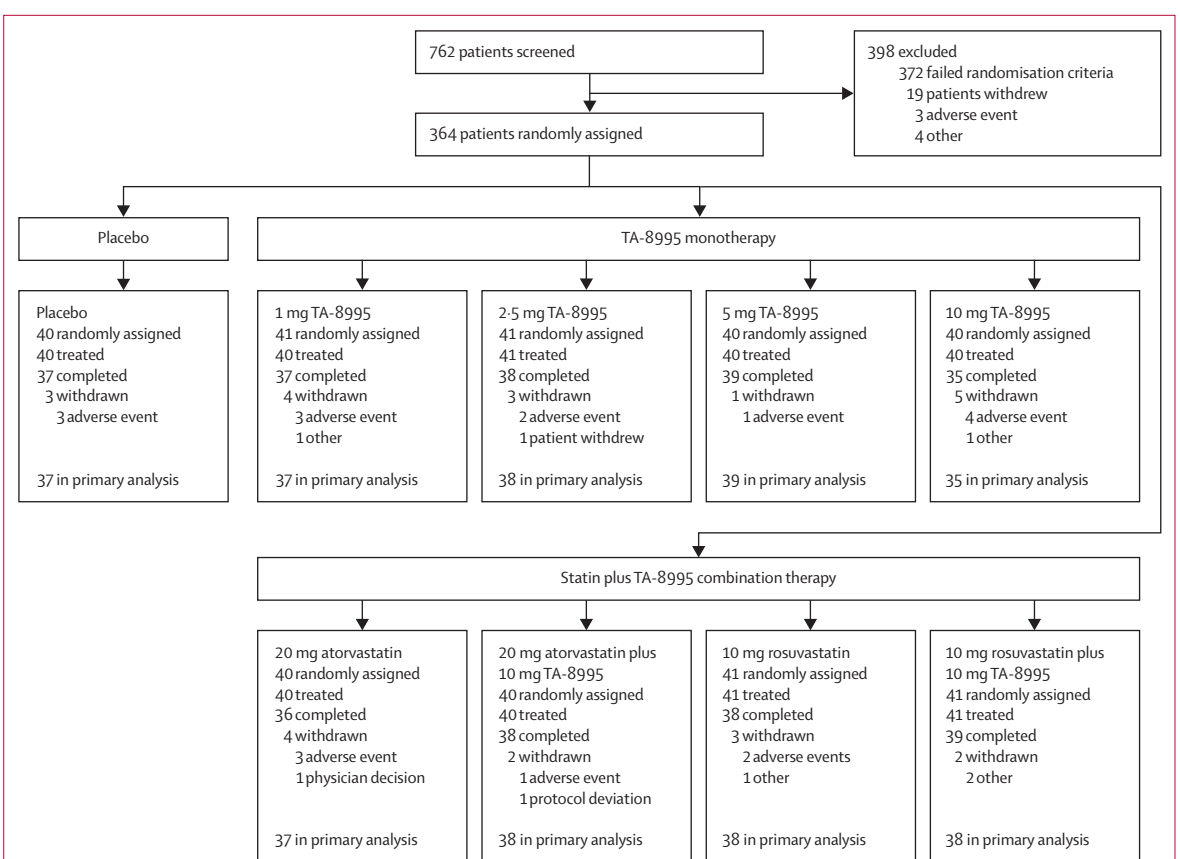


***Figure 1:*** **Trial profile**
The primary efficacy dataset included all patients who received at least one dose of study drug and had lipid measurements at baseline and week 12. All patients who received at least one dose of study drug were included in the safety analyses.

## Procedures

The TULIP study comprised a screening visit, followed by a run-in phase of 4 weeks (or 6 weeks for patients who needed washout of lipid-lowering treatment). All treatments were to be taken once a day with food for 12 weeks. During the double-blind treatment phase, visits were done at baseline (week 0) and at weeks 4, 8, and 12. Follow-up visits were done 2 and 8 weeks after the end of treatment. A data safety monitoring board ensured an independent review of safety-related variables during the trial. The appendix shows details of the assay methods.

See Online for appendix

| | Placebo (n=40) | 1 mg TA-8995 (n=41) | 2·5 mg TA-8995 (n=41) | 5 mg TA-8995 (n=40) | 10 mg TA-8995 (n=40) | 20 mg atorvastatin plus placebo (n=40) | 20 mg atorvastatin plus 10 mg TA-8995 (n=40) | 10 mg rosuvastatin plus placebo (n=41) | 10 mg rosuvastatin plus 10 mg TA-8995 (n=41) |
|---|---|---|---|---|---|---|---|---|---|
| Age (years) | 64·4 (6·6) | 65·8 (6·3) | 65·5 (6·9) | 64·9 (7·8) | 66·0 (5·0) | 64·0 (9·4) | 63·3 (9·1) | 64·7 (8·0) | 63·8 (6·1) |
| Sex (male) | 38 (95%) | 32 (78%) | 33 (81%) | 35 (88%) | 31 (78%) | 28 (70%) | 35 (88%) | 30 (73%) | 35 (85%) |
| BMI (kg/m²) | 26·0 (1·8) | 26·4 (2·7) | 25·6 (2·8) | 26·3 (2·7) | 25·9 (2·6) | 25·7 (2·4) | 26·0 (2·8) | 26·1 (2·7) | 26·3 (3·4) |
| Ethnic origin | | | | | | | | | |
| White | 40 (100%) | 41 (100%) | 41 (100%) | 39 (98%) | 38 (95%) | 39 (98%) | 39 (98%) | 40 (98%) | 40 (98%) |
| Other | 0 (0%) | 0 (0%) | 0 (0%) | 1 (3%) | 2 (5%) | 1 (3%) | 1 (3%) | 1 (2%) | 1 (2%) |
| Smoking status | | | | | | | | | |
| Current smoker | 6 (15%) | 2 (5%) | 6 (15%) | 5 (13%) | 7 (18%) | 2 (5%) | 5 (13%) | 4 (10%) | 8 (20%) |
| Non-smoker | 16 (40%) | 20 (49%) | 18 (44%) | 21 (53%) | 13 (33%) | 18 (45%) | 12 (30%) | 12 (29%) | 16 (39%) |
| Past smoker | 18 (45%) | 19 (46%) | 17 (42%) | 14 (35%) | 20 (50%) | 20 (50%) | 23 (58%) | 25 (61%) | 17 (42%) |
| Type 2 diabetes | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (3%) | 0 (0%) | 1 (3%) | 2 (5%) | 1 (2%) |

Data are mean (SD) or n (%).

***Table 1:*** **Baseline characteristics**

| | N | Baseline | Week 12 | Absolute change from baseline at week 12 | % change from baseline at week 12 | p value for % change from baseline | |
|---|---|---|---|---|---|---|---|
| | | | | | | TA-8995 monotherapy versus placebo | TA-8995 plus statin versus statin alone |
| **LDL cholesterol (mmol/L)** | | | | | | | |
| Placebo | 36 | 3·8 (0·5) | 3·7 (0·5) | −0·05, −0·09 (−0·34 to 0·22) | 0·8 (−3·4 to 4·9) | NA | NA |
| 1 mg TA-8995 | 36 | 3·6 (0·6) | 2·6 (0·6) | −0·98, −1·03 (−1·36 to −0·55) | −27·4 (−31·5 to −23·2) | <0·0001 | NA |
| 2·5 mg TA-8995 | 38 | 3·6 (0·5) | 2·4 (0·7) | −1·15, −1·17 (−1·52 to −0·64) | −32·7 (−36·8 to −28·6) | <0·0001 | NA |
| 5 mg TA-8995 | 39 | 3·5 (0·6) | 1·9 (0·5) | −1·62, −1·66 (−2·04 to −1·21) | −45·3 (−49·3 to −41·3) | <0·0001 | NA |
| 10 mg TA-8995 | 35 | 3·5 (0·6) | 1·9 (0·5) | −1·62, −1·66 (−1·92 to −1·14) | −45·3 (−49·4 to −41·1) | <0·0001 | NA |
| 20 mg atorvastatin | 37 | 3·8 (0·4) | 2·0 (0·4) | −1·77, −1·71 (−2·17 to −1·50) | −45·4 (−49·5 to −41·3) | NA | NA |
| 20 mg atorvastatin plus 10 mg TA-8995 | 38 | 3·5 (0·6) | 1·1 (0·4) | −2·37, −2·38 (−2·82 to −2·09) | −68·2 (−72·3 to −64·2) | NA | <0·0001 |
| 10 mg rosuvastatin | 38 | 3·7 (0·6) | 2·0 (0·4) | −1·72, −1·71 (−2·12 to −1·29) | −45·3 (−49·4 to −41·3) | NA | NA |
| 10 mg rosuvastatin plus 10 mg TA-8995 | 37 | 3·6 (0·6) | 1·3 (0·4) | −2·26, −2·26 (−2·54 to −2·02) | −63·3 (−67·4 to −59·2) | NA | <0·0001 |
| **HDL cholesterol (mmol/L)** | | | | | | | |
| Placebo | 37 | 1·3 (0·3) | 1·4 (0·3) | 0·02, 0·03 (−0·08 to 0·13) | 2·2 (−8·0 to 12·4) | NA | NA |
| 1 mg TA-8995 | 37 | 1·3 (0·2) | 2·4 (0·5) | 1·02, 1·03 (0·78 to 1·16) | 75·8 (65·5 to 86·1) | <0·0001 | NA |
| 2·5 mg TA-8995 | 38 | 1·4 (0·3) | 3·0 (0·7) | 1·66, 1·65 (1·40 to 1·97) | 124·3 (114·0 to 134·5) | <0·0001 | NA |
| 5 mg TA-8995 | 39 | 1·3 (0·2) | 3·3 (0·5) | 2·01, 1·99 (1·68 to 2·28) | 157·1 (147·0 to 167·1) | <0·0001 | NA |
| 10 mg TA-8995 | 35 | 1·3 (0·3) | 3·6 (0·6) | 2·30, 2·17 (1·94 to 2·59) | 179·0 (168·6 to 189·4) | <0·0001 | NA |
| 20 mg atorvastatin | 37 | 1·4 (0·2) | 1·4 (0·3) | 0·01, 0·03 (−0·10 to 0·08) | 5·7 (−4·7 to 16·0) | NA | NA |
| 20 mg atorvastatin plus 10 mg TA-8995 | 38 | 1·3 (0·3) | 3·3 (0·5) | 1·94, 1·98 (1·74 to 2·18) | 152·1 (141·9 to 162·2) | NA | <0·0001 |
| 10 mg rosuvastatin | 38 | 1·3 (0·3) | 1·4 (0·3) | 0·07, 0·04 (−0·06 to 0·23) | 7·1 (−3·0 to 17·2) | NA | NA |
| 10 mg rosuvastatin plus 10 mg TA-8995 | 38 | 1·4 (0·3) | 3·4 (0·5) | 2·07, 2·04 (1·76 to 2·38) | 157·5 (147·4 to 167·6) | NA | <0·0001 |

Data are n; mean (SD); mean, median (25–75th centiles); or least-squares mean (95% CI). N includes all patients who received at least one dose of study drug and had both baseline and week 12 data for each parameter.

***Table 2:*** **Summary of primary endpoints**

## Outcomes

The coprimary efficacy outcome parameters were percent change in LDL cholesterol and HDL cholesterol levels at week 12 compared with baseline. Secondary efficacy assessments included fasted total cholesterol, triglycerides, apolipoproteins A-I, B, and E and lipoprotein(a). Additional endpoints included CETP plasma concentrations, CETP activity, and homeostatic model assessment of insulin resistance (HOMA-IR). Cholesterol efflux capacity, an exploratory outcome, was measured according to the method described by Khera and colleagues[6,7] in patients receiving either placebo, 1 mg TA-8995, 10 mg TA-8995, or 10 mg TA-8995 plus 10 mg rosuvastatin.

Safety was assessed throughout the trial by monitoring adverse events, concomitant drug use, 12-lead electrocardiographs, vital signs, laboratory safety assessments,

| | N | Baseline | Week 12 | Absolute change from baseline at week 12 | % change from baseline at week 12 | p value for % change from baseline | |
|---|---|---|---|---|---|---|---|
| | | | | | | TA-8995 monotherapy versus placebo | TA-8995 + statin versus statin alone |
| **Triglycerides (mmol/L)** | | | | | | | |
| Placebo | 37 | 1·4 (0·6) | 1·3 (0·6) | −0·07, −0·12 (−0·36 to 0·07) | −3·0 (−13·3, 7·4) | NA | NA |
| 1 mg TA-8995 | 37 | 1·4 (0·5) | 1·1 (0·4) | −0·30, −0·19 (−0·46 to −0·03) | −17·5 (−27·9, −7·1) | 0·0524 | NA |
| 2·5 mg TA-8995 | 38 | 1·4 (0·8) | 1·2 (0·4) | −0·26, −0·12 (−0·43 to 0·05) | −11·8 (−22·1, −1·5) | 0·2347 | NA |
| 5 mg TA-8995 | 39 | 1·7 (1·0) | 1·3 (0·5) | −0·38, −0·14 (−0·64 to 0·06) | −7·6 (−17·8, 2·5) | 0·5274 | NA |
| 10 mg TA-8995 | 35 | 1·7 (0·7) | 1·5 (0·9) | −0·19, −0·12 (−0·59 to 0·16) | −5·7 (−16·3, 4·9) | 0·7179 | NA |
| 20 mg atorvastatin | 37 | 1·4 (0·5) | 1·0 (0·3) | −0·39, −0·34 (−0·51 to −0·25) | −25·2 (−35·6, −14·7) | NA | NA |
| 20 mg atorvastatin plus 10 mg TA-8995 | 38 | 1·3 (0·6) | 1·0 (0·4) | −0·32, −0·24 (−0·49 to 0·02) | −18·0 (−28·3, −7·7) | NA | 0·3355 |
| 10 mg rosuvastatin | 38 | 1·6 (0·7) | 1·3 (1·2) | −0·28, −0·38 (−0·69 to −0·09) | −14·9 (−25·2, −4·7) | NA | NA |
| 10 mg rosuvastatin plus 10 mg TA-8995 | 38 | 1·4 (0·6) | 1·0 (0·3) | −0·34, −0·30 (−0·58 to −0·01) | −11·5 (−21·7, −1·2) | NA | 0·6408 |
| **Total cholesterol (mmol/L)** | | | | | | | |
| Placebo | 37 | 5·8 (0·5) | 5·8 (0·6) | −0·03, −0·05 (−0·34 to 0·28) | 1·1 (−2·6, 4·7) | NA | NA |
| 1 mg TA-8995 | 37 | 5·6 (0·7) | 5·5 (0·9) | −0·11, −0·13 (−0·52 to 0·36) | −2·0 (−5·6, 1·7) | 0·2507 | NA |
| 2·5 mg TA-8995 | 38 | 5·6 (0·7) | 5·9 (1·0) | 0·31, 0·43 (−0·31 to 0·98) | 5·8 (2·1, 9·4) | 0·0756 | NA |
| 5 mg TA-8995 | 39 | 5·6 (0·7) | 5·7 (0·8) | 0·11, 0·16 (−0·39 to 0·57) | 2·2 (−1·3, 5·8) | 0·6560 | NA |
| 10 mg TA-8995 | 35 | 5·7 (0·6) | 6·1 (0·7) | 0·44, 0·47 (−0·15 to 0·99) | 8·5 (4·8, 12·1) | 0·0056 | NA |
| 20 mg atorvastatin | 37 | 5·9 (0·5) | 3·9 (0·5) | −1·97, −2·02 (−2·49 to −1·53) | −31·7 (−35·4, −28·0) | NA | NA |
| 20 mg atorvastatin plus 10 mg TA-8995 | 38 | 5·5 (0·7) | 4·8 (0·6) | −0·69, −0·77 (−1·12 to −0·36) | −13·2 (−16·8, −9·6) | NA | <0·0001 |
| 10 mg rosuvastatin | 38 | 5·8 (0·7) | 4·0 (0·5) | −1·88, −1·90 (−2·28 to −1·58) | −30·7 (−34·3, −27·1) | NA | NA |
| 10 mg rosuvastatin plus 10 mg TA-8995 | 38 | 5·6 (0·7) | 5·2 (0·8) | −0·46, −0·47 (−0·90 to 0·05) | −8·2 (−11·8, −4·6) | NA | <0·0001 |
| **Apolipoprotein A-1 (g/L)** | | | | | | | |
| Placebo | 37 | 1·4 (0·2) | 1·5 (0·2) | 0·02, 0·05 (−0·11 to 0·12) | 2·5 (−2·4, 7·4) | NA | NA |
| 1 mg TA-8995 | 37 | 1·4 (0·2) | 1·9 (0·3) | 0·45, 0·45 (−0·28 to 0·61) | 31·2 (26·2, 36·1) | <0·0001 | NA |
| 2·5 mg TA-8995 | 38 | 1·5 (0·2) | 2·2 (0·4) | 0·69, 0·73 (0·49 to 0·85) | 49·0 (44·1, 53·9) | <0·0001 | NA |
| 5 mg TA-8995 | 39 | 1·4 (0·2) | 2·2 (0·3) | 0·81, 0·82 (0·64 to 0·95) | 57·5 (52·7, 62·3) | <0·0001 | NA |
| 10 mg TA-8995 | 35 | 1·4 (0·2) | 2·3 (0·2) | 0·90, 0·86 (0·73 to 1·03) | 63·4 (58·3, 68·4) | <0·0001 | NA |
| 20 mg atorvastatin | 37 | 1·5 (0·2) | 1·5 (0·2) | −0·03, −0·04 (−0·15 to 0·10) | 0·8 (−4·2, 5·8) | NA | NA |
| 20 mg atorvastatin plus 10 mg TA-8995 | 38 | 1·4 (0·2) | 2·1 (0·2) | 0·74, 0·72 (0·62 to 0·91) | 52·7 (47·8, 57·5) | NA | <0·0001 |
| 10 mg rosuvastatin | 38 | 1·4 (0·2) | 1·5 (0·2) | 0·04, 0·05 (−0·06 to 0·15) | 4·3 (−0·6, 9·2) | NA | NA |
| 10 mg rosuvastatin plus 10 mg TA-8995 | 38 | 1·4 (0·2) | 2·2 (0·2) | 0·77, 0·75 (0·66 to 0·88) | 55·8 (50·9, 60·6) | NA | <0·0001 |
| **Apolipoprotein B (g/L)** | | | | | | | |
| Placebo | 37 | 1·0 (0·1) | 1·0 (0·1) | −0·01, −0·02 (−0·09 to 0·06) | 1·1 (−2·5, 4·7) | NA | NA |
| 1 mg TA-8995 | 37 | 1·0 (0·2) | 0·8 (0·1) | −0·20, −0·18 (−0·31 to −0·11) | −20·0 (−23·6, −16·4) | <0·0001 | NA |
| 2·5 mg TA-8995 | 38 | 1·0 (0·2) | 0·7 (0·1) | −0·25, −0·23 (−0·33 to −0·14) | −24·6 (−28·2, −21·0) | <0·0001 | NA |
| 5 mg TA-8995 | 39 | 1·0 (0·2) | 0·7 (0·1) | −0·35, −0·37 (−0·45 to −0·24) | −33·6 (−37·1, −30·1) | <0·0001 | NA |
| 10 mg TA-8995 | 35 | 1·0 (0·2) | 0·6 (0·1) | −0·35, −0·34 (−0·44 to −0·21) | −33·7 (−37·3, −30·0) | <0·0001 | NA |
| 20 mg atorvastatin | 37 | 1·0 (0·1) | 0·6 (0·1) | −0·40, −0·41 (−0·47 to −0·31) | −37·4 (−41·0, −33·8) | NA | NA |
| 20 mg atorvastatin plus 10 mg TA-8995 | 38 | 1·0 (0·2) | 0·5 (0·1) | −0·51, −0·51 (−0·61 to −0·41) | −50·1 (−53·7, −46·6) | NA | <0·0001 |
| 10 mg rosuvastatin | 38 | 1·0 (0·1) | 0·7 (0·1) | −0·37, −0·36 (−0·44 to −0·27) | −34·5 (−38·0, −30·9) | NA | NA |
| 10 mg rosuvastatin plus 10 mg TA-8995 | 38 | 1·0 (0·1) | 0·5 (0·1) | −0·47, −0·45 (−0·53 to −0·39) | −46·3 (−49·9, −42·8) | NA | <0·0001 |

(Table 3 continues on next page)

and physical examinations. Additional safety assessments included plasma aldosterone, salivary cortisol, high-sensitivity C-reactive protein, and endothelin-1 concentrations. Blood samples were also collected for pharmacokinetic analysis.

### Statistical analysis

The primary efficacy analysis of the percent change in HDL cholesterol and LDL cholesterol from baseline to week 12 was done with a restricted maximum likelihood mixed model for repeated measures approach. Analysis included fixed categorical effects of treatment, visit and treatment-by-visit interaction, and a continuous fixed covariate for baseline HDL cholesterol or LDL cholesterol score. Least-squares means, standard errors and two-tailed 95% confidence intervals for each treatment group and for pairwise comparisons between TA-8995 doses and placebo, between TA-8995 plus atorvastatin and atorvastatin alone, and between TA-8995 plus rosuvastatin and rosuvastatin alone were provided. Because there were two coprimary efficacy variables, we used a closed testing procedure to control the family-wise error. No interim analyses were planned or undertaken.

The sample size of 37 completed patients per treatment group was intended to provide 88% power to detect a 22·5% (standard deviation [SD] 30%) increase in HDL cholesterol compared with statin alone. This sample size with an assumed 10% (SD 15%) greater decrease in LDL cholesterol for the investigational product compared with placebo was expected to provide a power of 80%. All tests were two-sided with a significance of 0·05. To allow for a 10–15% dropout rate, 378 patients were planned. All analyses were done with SAS (version 9.2).

The trial protocol was registered on ClinicalTrials.gov, number NCT01970215.

### Role of the funding source

The funder was involved in the design of the study and in collection, management, and analysis of the data, in conjunction with the steering committee. The initial draft of the report was prepared by PR and PJB. GKH in conjunction with the other authors had the main responsibility for the decision to submit for publication. The authors vouch for the accuracy and completeness of the data and analyses as presented.

## Results

Between August, 2013, and July, 2014, 364 patients were randomly assigned and received at least one dose of study treatment, and 337 (93%) completed the trial (figure 1). Primary outcome data (LDL cholesterol and

| | N | Baseline | Week 12 | Absolute change from baseline at week 12 | % change from baseline at week 12 | p value for % change from baseline | |
|---|---|---|---|---|---|---|---|
| | | | | | | TA-8995 monotherapy versus placebo | TA-8995 + statin versus statin alone |
| (Continued from previous page) | | | | | | | |
| **Apolipoprotein E (g/L)** | | | | | | | |
| Placebo | 37 | 0·04 (0·01) | 0·04 (0·01) | 0·001, 0·000 (–0·002 to 0·003) | 3·2 (–7·8, 14·3) | NA | NA |
| 1 mg TA-8995 | 37 | 0·04 (0·01) | 0·05 (0·02) | 0·008, 0·004 (–0·001 to 0·012) | 19·3 (8·2, 30·4) | 0·0446 | NA |
| 2·5 mg TA-8995 | 38 | 0·04 (0·01) | 0·05 (0·02) | 0·012, 0·008 (0·003 to 0·018) | 33·4 (22·3, 44·4) | 0·0002 | NA |
| 5 mg TA-8995 | 39 | 0·04 (0·01) | 0·05 (0·02) | 0·012, 0·010 (0·004 to 0·024) | 37·8 (27·0, 48·6) | <0·0001 | NA |
| 10 mg TA-8995 | 35 | 0·04 (0·01) | 0·06 (0·02) | 0·020, 0·017 (0·009 to 0·028) | 57·0 (45·8, 68·2) | <0·0001 | NA |
| 20 mg atorva | 37 | 0·04 (0·01) | 0·03 (0·01) | –0·008, –0·008 (–0·010 to –0·004) | –20·7 (–31·8, –9·5) | NA | NA |
| 20 mg atorva + 10 mg TA-8995 | 38 | 0·04 (0·01) | 0·04 (0·02) | 0·006, 0·006 (–0·005 to 0·013) | 17·9 (7·0, 28·8) | NA | <0·0001 |
| 10 mg rosuvastatin | 38 | 0·04 (0·01) | 0·03 (0·01) | –0·007, –0·007 (–0·012 to –0·002) | –15·9 (–26·7, –4·9) | NA | NA |
| 10 mg rosuvastatin plus 10 mg TA-8995 | 38 | 0·04 (0·01) | 0·06 (0·02) | 0·019, 0·017 (0·008 to 0·028) | 54·6 (43·7, 65·5) | NA | <0·0001 |
| **Lipoprotein(a) (nmol/L)** | | | | | | | |
| Placebo | 37 | 51·8 (61·8) | 49·4 (61·9) | –2·4, –1·0 (–7 to 0) | –1·8 (–10·7 to 7·2) | NA | NA |
| 1 mg TA-8995 | 37 | 47·3 (55·5) | 39·5 (55·4) | –7·8, –5·0 (–10 to –2) | –29·5 (–38·6 to –20·4) | <0·0001 | NA |
| 2·5 mg TA-8995 | 38 | 44·6 (53·2) | 33·6 (44·1) | –11·0, –5·5 (–16 to 0) | –26·7 (–35·7 to –17·7) | 0·0001 | NA |
| 5 mg TA-8995 | 39 | 42·2 (54·3) | 23·7 (37·7) | –18·5, –11·0 (–32 to –1) | –36·9 (–45·7 to –28·1) | <0·0001 | NA |
| 10 mg TA-8995 | 35 | 44·4 (65·6) | 27·6 (48·1) | –16·8, –10·0 (–25 to 0) | –33·4 (–42·5 to –24·4) | <0·0001 | NA |
| 20 mg atorvastatin | 37 | 31·6 (41·3) | 30·1 (38·9) | –1·5, –1·0 (–3 to 1) | –3·6 (–12·7 to 5·5) | NA | NA |
| 20 mg atorvastatin plus 10 mg TA-8995 | 38 | 36·6 (42·7) | 28·5 (40·5) | –8·1, –3·5 (–11 to 0) | –25·0 (–33·8 to –16·1) | NA | 0·0011 |
| 10 mg rosuvastatin | 38 | 38·8 (54·8) | 37·5 (58·0) | –1·3, 0·0 (–3 to 0) | –7·9 (–16·8 to 1·0) | NA | NA |
| 10 mg rosuvastatin plus 10 mg TA-8995 | 38 | 62·3 (74·4) | 55·9 (78·6) | –6·3, –3·0 (–17 to 0) | –25·4 (–34·3 to –16·5) | NA | 0·0064 |

Data are n; mean (SD); mean, median (25–75th centiles); or least-squares mean (95% CI). N includes all patients who received at least one dose of study drug and had both baseline and week 12 data.

*Table 3:* **Summary of secondary endpoints**

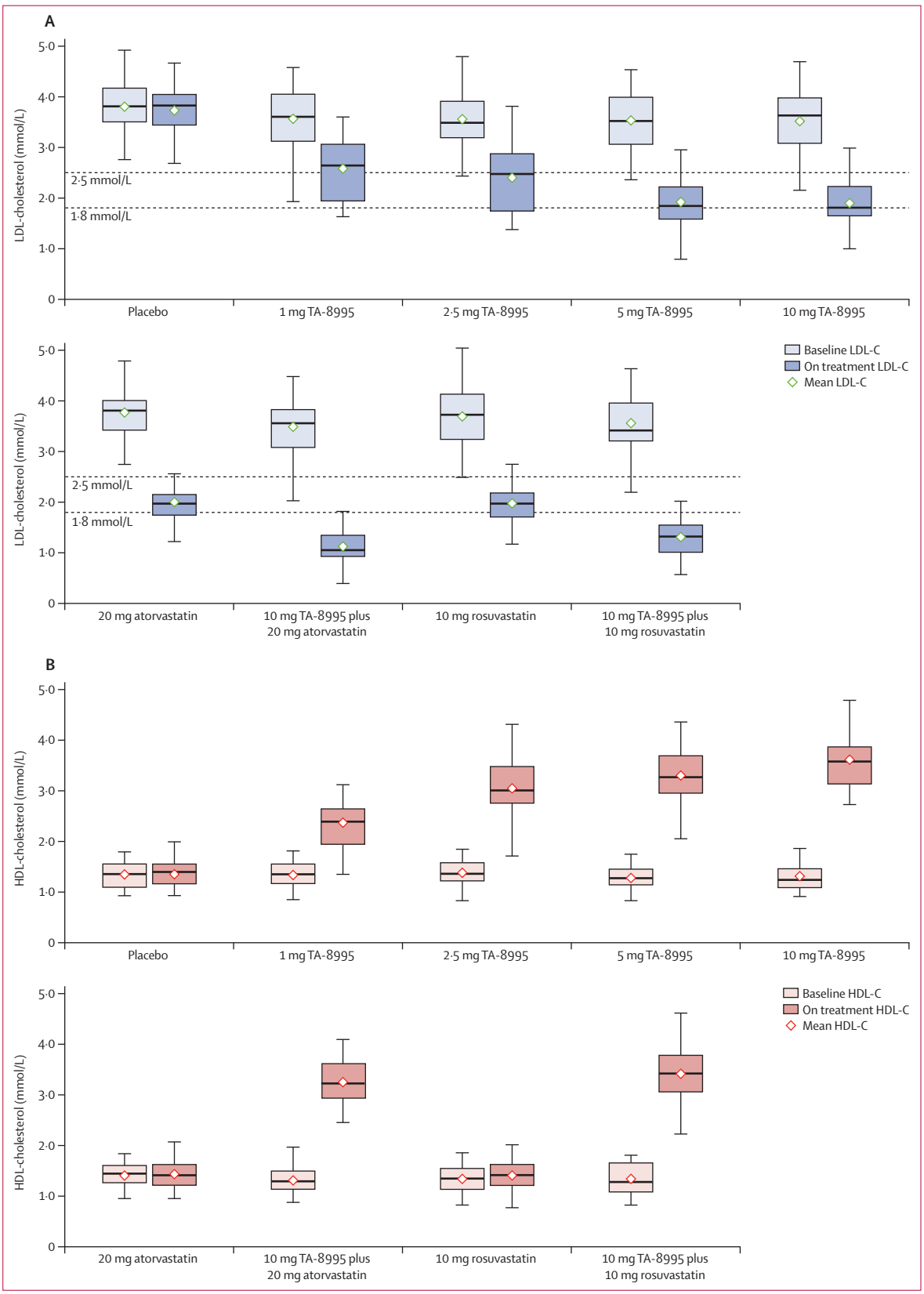


***Figure 2*: Baseline and week 12 data for LDL (A) and HDL (B)**
Boxes show the 25th and 75th percentiles, whiskers show the minimum and maximum values, horizontal lines show the median, and green circles show the mean. The data only include patients who had both baseline and week 12 data. The changes from baseline for all active treatments showed significant differences from placebo at week 12 (p<0·0001).

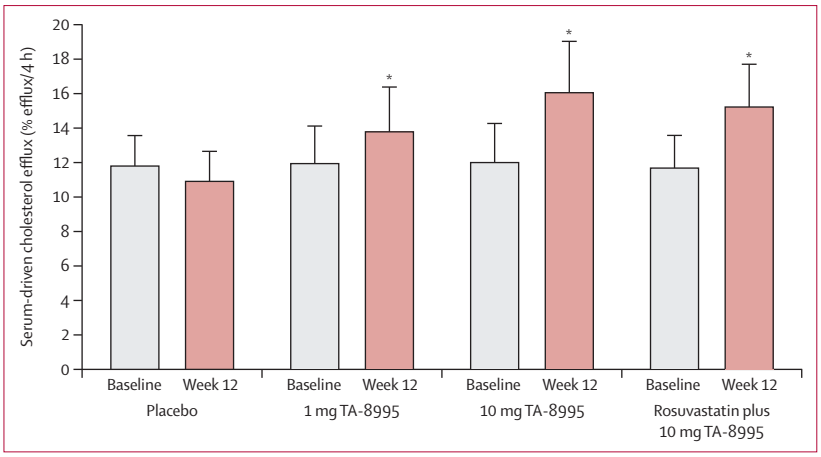


***Figure 3:*** **Baseline and week 12 data for serum-driven cholesterol efflux**
Bars are means and error bars are standard deviations. The baseline data only include patients who had both baseline and week 12 data. The changes from baseline for all active treatments showed significant differences from placebo at week 12 (*p<0·0001).

HDL cholesterol levels at week 12) were available in 35 to 38 patients per treatment group. Table 1 shows baseline characteristics across all treatment groups. Most participants were white men with a mean age of 65 years (range 22–75). Mean baseline LDL cholesterol concentration was 3·60 mmol/L (SD 0·57) and HDL cholesterol was 1·35 mmol/L (0·26) and these did not differ across treatment groups (table 1).

Table 2 shows the primary efficacy outcomes. At week 12, LDL cholesterol concentrations were reduced significantly by 27·4% in patients who received 1 mg TA-8995, 32·7% in those who received the 2·5 mg dose, 45·3% in those given the 5 mg dose, and 45·3% in those given the 10 mg dose (p<0·0001 for all). A daily dose of 20 mg atorvastatin resulted in a 45·4% decrease in LDL cholesterol, whereas we noted a 68·2% decrease in patients given 10 mg TA-8995 plus atorvastatin 20 mg (p<0·0001), which translates into an additional 50·2% reduction in LDL cholesterol in patients randomly assigned to combination therapy. We noted similar results in patients given 10 mg rosuvastatin (LDL cholesterol decrease 45·3%) or 10 mg rosuvastatin plus 10 mg TA-8995 (LDL cholesterol decrease of 63·3%), which corresponds to an additional 39·8% lowering of LDL cholesterol in patients given TA-8995 combined with rosuvastatin. Figure 2 shows the results for the primary outcomes. When TA-8995 was provided as monotherapy, 95% of patients achieved an LDL cholesterol concentration lower than 2·5 mmol/L at both the daily 5 mg and 10 mg doses, whereas 65% of patients given the 5 mg dose achieved an LDL cholesterol concentration lower than 1·8 mmol/L and 63% of those given the 10 mg dose.

HDL cholesterol was increased significantly from baseline to week 12 by 75·8% in patients given 1 mg TA-8995 a day, 124·3% in those given 2·5 mg, 157·1% in those given 5 mg, and 179·0% in those given 10 mg (p<0·0001). We noted these effects at the first post-randomisation visit (week 4) and the effects remained present throughout the treatment period (data not shown). TA-8995 was equally effective when given as monotherapy or on top of statin treatment. HDL cholesterol increased by 152·1% in patients receiving 10 mg TA-8995 combined with 20 mg atorvastatin and 157·5% in patients receiving 10 mg TA-8995 combined with 10 mg rosuvastatin (p<0·0001 for both).

Table 3 shows the secondary efficacy outcomes. TA-8995 had no significant effect on plasma triglyceride or total cholesterol levels. However, monotherapy with TA-8995 resulted in substantial dose-dependent increases in apoA-1 and apoE concentrations, all of which were significant compared with baseline (p<0·0001), except for the apoE change in patients given 1 mg TA-8995 (p=0·0446) and 2·5 mg TA-8995 (p=0·0002). Additionally, apoB concentrations were reduced by 20·0% to 33·7% in patients receiving TA-8995 as monotherapy (p<0·0001), whereas in patients receiving TA-8995 combined with atorvastatin, concentrations were reduced by 50·1% and in patients receiving TA-8995 combined with rosuvastatin apoB by 46·3% (p<0·0001).

The different doses of TA-8995, either as monotherapy or combined with a statin resulted in reductions in lipoprotein(a) ranging from 26·7% to 36·9% (p<0·0064), whereas monotherapy with a statin resulted in reductions in lipoprotein(a) of 3·6% and 7·9% (table 3). Monotherapy with TA-8995 reduced CETP activity by up to 84·9% (p<0·0001; appendix).

Serum-mediated cholesterol efflux was measured at baseline and at week 12 as an exploratory outcome. We noted a 7% reduction in serum-mediated cell cholesterol efflux (figure 3) in patients given placebo. By contrast, the ability of serum to promote cholesterol efflux was increased by 16·9% (p<0·0001) in patients given 1 mg TA-8995, whereas treatment with the 10 mg dose resulted in a 36·7% increase in serum-mediated cholesterol efflux (p< 0·0001; figure 3).

TA-8995 was well tolerated and the percentage of patients withdrawing because of adverse events was low and similar across treatment groups (appendix). The most common adverse events in the TA-8995 monotherapy group were nasopharyngitis and headache. Most (122/127 [96%]) adverse events were classified as mild or moderate. Eight patients had serious adverse events during the study but none were deemed to be treatment-related. We noted no effect of TA-8995 (whether given as monotherapy or in combination with a statin) on any laboratory safety parameter including serum aldosterone, salivary cortisol, high sensitivity C-reactive protein or endothelin-1. We analysed the data for each treatment group separately and combined for all patients receiving TA-8995 monotherapy (appendix). TA-8995 had no effect on serum electrolyte concentrations or blood pressure (appendix). TA-8995 treatment did not affect HOMA-IR (appendix).

The mean trough concentrations of TA-8995 were the same at weeks 8 and 12, which suggests that steady state conditions had been achieved by week 8 (data not shown).

After cessation of dosing, concentrations decreased rapidly and by week 20 (8 weeks after the last dose), concentrations of TA-8995 (given either as monotherapy or in combination with a statin) were less than 3% of the trough levels during treatment, which emphasises that TA-8995 does not accumulate during a 12-week dosing period.

## Discussion

In this phase 2 study we showed that administration of TA-8995, a new CETP inhibitor, reduced LDL cholesterol levels by 45·3% and apoB levels by 33·7%, whereas HDL cholesterol levels increased by up to 179·1% and apoA-1 levels by up to 63·4%. In combination with statins, 10 mg TA-8995 conferred an additional decrease of LDL cholesterol by 39·8% to 50·2% (panel).

CETP promotes the transfer of cholesteryl esters (the main form of cholesterol in plasma) from non-atherogenic HDL particles, where they are formed, to particles in lipoprotein fractions (including LDL) that cause atherosclerosis. Inhibition of CETP blocks this transfer and reduces the concentration of cholesterol not only in LDL, but also in other atherogenic lipoproteins. The hypothesis that CETP inhibition might be antiatherogenic is supported by results of genomic studies showing that carriers of CETP polymorphisms associated with low CETP activity are at a decreased risk of future cardiovascular events.[8,9]

The ILLUMINATE study[3] was the first clinical trial to address the effect of lowering CETP on cardiovascular disease outcome. In this study, torcetrapib, a CETP inhibitor that reduced LDL cholesterol levels by roughly 25% and raised HDL cholesterol levels by about 50%, did not reduce cardiovascular risk. In fact, torcetrapib increased both non-fatal and fatal cardiovascular events and also increased death from non-cardiovascular causes. The explanation for the adverse outcome is not fully understood, but could have been the consequence of serious off-target effects of this compound. Investigators noted a significant increase in blood pressure in patients given torcetapib. Results of subsequent studies showed that torcetrapib also increased the synthesis and secretion of both aldosterone and cortisol from adrenal cortical cells in tissue culture and increased expression of endothelin-1 in the artery wall.[10,11] The presence of these off-target effects made it impossible to draw any meaningful conclusions regarding the possible antiatherogenic potential of CETP inhibition.

TA-8995 seems to be free of the adverse effects of torcetrapib and, at low doses, effectively reduces LDL cholesterol, apoB, and lipoprotein(a). The magnitude of the reductions induced by treatment with TA-8995 suggests that this drug has the potential to provide substantial reductions in cardiovascular risk. Findings of previous intervention studies have shown that a statin-induced decrease in LDL cholesterol and apoB has a beneficial effect on cardiovascular disease outcome[12] and the clinical relevance of non-statin induced LDL cholesterol lowering has recently been established in the IMPROVE-IT study.[13] Lipoprotein(a) concentrations are positively associated with incident cardiovascular disease events, but whether lipoprotein(a) lowering results in cardiovascular disease risk reduction is unknown.[14]

Although CETP inhibitors were initially designated HDL cholesterol-increasing agents, TA-8995 potently reduces the concentrations of atherogenic lipoproteins such as LDL, either as monotherapy or in combination with statin treatment. The major increase in concentrations of HDL cholesterol and apoA-1 with TA-8995 might have an additional beneficial effect. The role of HDL cholesterol in cardiovascular disease risk is not completely understood and it remains to be established whether a therapeutic increase of HDL cholesterol and HDL particle numbers will translate into a reduced cardiovascular disease risk.[15] Dalcetrapib, a rather weak CETP inhibitor that increased HDL cholesterol concentrations by about 30% and had no effect on LDL cholesterol levels, was not associated with cardiovascular events or cardiovascular-related adverse events.[4]

The failure of dalcetrapib could have been the consequence of the inability of this agent to reduce the levels of LDL cholesterol or to sufficiently stimulate cholesterol efflux. Cholesterol efflux has been studied by Ray and coworkers[16] who noted that total cholesterol efflux capacity, assessed by the same method used in the present TULIP trial, increased by 9·5% in patients randomly assigned to receive 600 mg dalcetrapib once a day for 4 weeks. In patients given evacetrapib (at a dose range of 30–500 mg per day) the mean cholesterol efflux increased by 28%.[17] A daily dose of 10 mg TA-8995 resulted in a 36·7% increase in the ability of serum to promote cell cholesterol efflux. Recent evidence that cholesterol efflux capacity has a strong inverse correlation with incident cardiovascular events suggests that this property of TA-8995 might provide additional protection against

***Panel:* Research in context**

**Systematic review**

In December, 2014, we searched Pubmed to identify studies published since 2006 in any language on CETP, cardiovascular disease, and (novel) therapeutic agents. The following terms were used: "CETP AND treatment", and "dyslipidemia AND randomised controlled trial". We only included studies in human beings.

**Interpretation**

Many patients do not reach optimum LDL cholesterol levels despite a maximally tolerated dose of statins. Further LDL cholesterol lowering is warranted in these individuals and CETP inhibition causes such an effect. Our findings show that TA-8995, a novel CETP inhibitor, has a beneficial effect on lipids and lipoproteins; LDL cholesterol decreased by 45·3% and apoB levels by 33·7%, whereas HDL cholesterol concentrations increased by up to 179·1% and apoA-I by 63·4%. Lastly, cholesterol efflux capacity increased by 36·7% in patients randomly assigned to 10 mg TA-8995. All these effects were similar in patients on monotherapy or in combination with a statin. No related serious adverse events were reported and the drug was well tolerated. These findings are important because they provide clinicians with the evidence that CETP inhibition with TA-8995 is an effective LDL cholesterol lowering and HDL cholesterol increasing treatment with the aim to prevent cardiovascular disease.

cardiovascular events.[18] However, the hypothesis that a therapeutic increase of cholesterol efflux affects cardiovascular outcome remains to be validated in clinical studies. It also needs to be established whether a selected patient group characterised by an untoward cardiometabolic background (ie, patients with diabetes with high CETP) might differentially benefit from CETP inhibitor treatment.

CETP inhibitors are lipophilic by nature and it has been recently reported that anacetrapib is retained in adipose tissue and might remain detectable in serum years after discontinuation of dosing.[19] By contrast, TA-8995 is not retained in adipose tissue and is rapidly eliminated after discontinuation of dosing. Furthermore, TA-8995 was not detected in fat or liver tissue after 9 months chronic dosing of cynomolgus monkeys at a supratherapeutic dose (data not shown).

In conclusion, we report the effects of a new CETP inhibitor that potently lowers the concentrations of LDL cholesterol, apoB, non-HDL cholesterol, and lipoprotein(a) either as monotherapy or in combination with a statin. As a potential additive beneficial effect, TA-8995 induces a significant increase of plasma apoA-I concentrationss and a substantial increase in the ability to promote cholesterol efflux. The translation of the antiatherogenic potential of TA-8995 recorded in this study into a reduction of future cardiovascular events warrants formal testing in a cardiovascular outcome trial.

#### Contributors

JJPK, SJHvD, PR, and JF (Dezima, Naarden, the Netherlands) designed the study in collaboration with HBB and PJB. JJPK, HBB, and PJB were members of the steering committee. PR was responsible for the study conduct and coordination of all statistical analyses, data review and interpretation, report review and revisions. This report was mainly written by GKH, PR, PJB, and JJPK, with assistance from SJHvD and DJR, and was critically reviewed and subsequently approved by all authors. The efflux assays were done under supervision of DS and DJR.

#### Declaration of interests

GKH reports that his institution has received funding from Dezima, Amgen, Pfizer, Sanofi, Regeneron, AstraZeneca, Genzyme, Cerenis, Synageva, Roche, ISIS pharmaceuticals, Kowa, and Merck for undertaking clinical trials related to various forms of lipid-lowering medication and consulting fees from Amgen, Pfizer, Roche, and Sanofi. JJP reports personal fees from Dezima Pharmaceuticals during the conduct of the study; personal fees from Cerenis, The Medicines Company, CSL Behring, Amgen, Sanofi, Regeneron, Eli Lilly, Genzyme, Aegerion, Esperion, AstraZeneca, Omthera, Pronova, Vascular Biogenics, Boehringer Ingelheim, Catabasis, AtheroNova, UniQure, Novartis, Merck, Isis Pharmaceuticals, and Kowa. PR and JF are employees of Xention, the sponsor of the TULIP study. SJHvD is a managing partner at Forbion Capital Partners, which owns equity in Dezima Pharma. PJB reports fees from Dezima, during the conduct of the study; personal fees from AstraZeneca, AMGEN, Novartis, CSL-Behring, Kowa, Merck, and Sanofi-Regeneron, outside the submitted work and grants and personal fees from Pfizer.

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