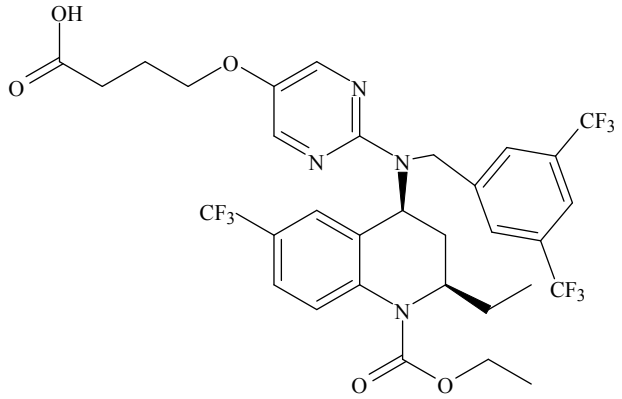
P-12186
Nuevo capítulo reivindicatorio
Septiembre 20, 2018

REIVINDICACIONES

1. Una composición farmacéutica, caracterizada porque comprende 1 a 25 mg del compuesto:



(a partir de ahora: Compuesto A) o una sal de calcio, potasio o sodio del mismo.

2. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende de 5 mg a 10 mg de Compuesto A, o una sal de calcio, potasio o sodio del mismo.

3. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 1 mg de Compuesto A, o una sal de calcio, potasio o sodio del mismo.

4. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 2.5 mg de Compuesto A, o una sal de calcio, potasio o sodio del mismo.

5. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 5 mg de Compuesto A, o una sal de calcio, potasio o sodio del mismo.

6. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 10 mg de Compuesto A, o una sal de calcio, potasio o sodio del mismo.

7. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 25 mg de Compuesto A, o una sal de calcio, potasio o sodio del mismo.

8. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 1 mg de sal de calcio del Compuesto A.

9. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 2.5 mg de sal de calcio del Compuesto A.

10. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 5 mg de sal de calcio del Compuesto A.

11. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 10 mg de sal de calcio del Compuesto A.

12. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 25 mg de sal de calcio del Compuesto A.

13. La composición farmacéutica de conformidad con cualquiera de las reivindicaciones 1 a 12, caracterizada porque la sal de calcio es la sal de hemicalcio.

14. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 1 mg de sal de potasio del Compuesto A.

15. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 2.5 mg de sal de potasio del Compuesto A.

16. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 5 mg de sal de potasio del Compuesto A.

17. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 10 mg de sal de potasio del Compuesto A.

18. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 25 mg de sal de potasio del Compuesto A.

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24. La composición farmacéutica de conformidad con cualquiera de las reivindicaciones 1-23, caracterizada porque la composición se formula como una forma de dosificación unitaria individual, en donde la forma de dosificación unitaria individual es una forma de dosificación oral líquida o una forma de dosificación oral sólida, tal como un comprimido o cápsula.

Clarke, Modet & Cº
COLOMBIA

P-12186

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **NC2016/0000629**
Solicitud de patente a nombre de **DEZIMA PHARMA B.V.**

Yo, CAROLINA DAZA MONTALVO identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53, piso 3, obrando como apoderada de la sociedad **DEZIMA PHARMA B.V.**, domiciliada en Breda, Países Bajos, solicitante de la patente de la referencia, en respuesta al Oficio No. **7729** notificado por comunicación electrónica el 25 de junio de 2018 y relacionado con concepto técnico de fondo, me permito manifestar:

1. Modificaciones al capítulo reivindicatorio

En primer lugar, con fundamento en la facultad que confiere el Artículo 34 de la Decisión 486/00 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, me permito presentar junto con este memorial un nuevo capítulo reivindicatorio que consta de 24 reivindicaciones y reemplaza completamente al anteriormente presentado, cuya única modificación consiste en la inclusión de la materia de la reivindicación 25 anteriormente presentada en la reivindicación 24.

En cuanto a esta modificación, me permito decir que la misma no amplía de ninguna manera la materia objeto de la presente solicitud, y se realizó con el ánimo de superar las objeciones planteadas por el examinador en su concepto técnico.

2. Pago de tasas

En relación con el número de reivindicaciones, atentamente me permito comentar que no se adjunta tasa por reivindicaciones adicionales, toda vez que el nuevo capítulo reivindicatorio cuenta con menos cláusulas que el anteriormente presentado.

Por otra parte, me permito adjuntar recibo por concepto de pago de tasa para un nuevo examen de patentabilidad sobre el nuevo pliego reivindicatorio, según lo estipulado en la Resolución No. 3719 de 2016.

3. <u>Claridad y concisión del capítulo reivindicatorio</u>

Ahora bien, con relación a la claridad y concisión de las reivindicaciones, me permito manifestar que mediante el nuevo capítulo reivindicatorio quedan subsanadas la totalidad de las objeciones a este respecto, ya que las nuevas reivindicaciones proporcionan claridad y concisión a la invención reclamada, cuentan con pleno soporte en la descripción de la solicitud en estudio, y siguen las recomendaciones realizadas por el examinador en su concepto técnico. En particular, frente a cada objeción, me permito señalar lo siguiente:

3.1. «*La reivindicación 1 carece de sustento descriptivo toda vez que la solicitud adolece de ejemplos de formulaciones, métodos de elaboración de las mismas y de ensayos relacionados con la valoración de formulaciones específicas que hayan permitido resolver algún problema técnico.*»

Frente a lo anterior, amablemente me permito reiterar que una persona normalmente versada en la materia sería capaz de diseñar fácilmente una composición farmacéutica del Compuesto A a la luz de las enseñanzas del documento WO 2005/095409.

El documento D1 citado por el examinador en su concepto técnico, que es equivalente a la solicitud internacional publicada WO 2005/095409, es referenciado en la descripción de la presente solicitud, *véase* la página 21, líneas 20-23. Específicamente, el documento WO 2005/095409 desvela el método de preparación del Compuesto A y sus sales (sodio, calcio y potasio). *Véase* el Ejemplo 177, páginas 167-169 del documento WO 2005/095409, que describe la preparación del compuesto A; el Ejemplo 178, página 169 del documento WO 2005/095409, que describe la preparación de la sal de sodio del Compuesto A; el Ejemplo 179, páginas 169-170 del documento WO 2005/095409, que describe la preparación de la sal de calcio del Compuesto A; y el Ejemplo 180, página 170 del documento WO 2005/095409, que describe la preparación de la sal de potasio del Compuesto A.

En las presente reivindicaciones no se está reclamando una formulación específica. Una persona normalmente versada en la materia es capaz de seleccionar excipientes

adecuados y sus cantidades para diseñar una composición farmacéutica fácilmente, ya que esto hace parte de su conocimiento general. Por tanto, me permito solicitar a ese Despacho que la objeción a este respecto sea retirada.

3.2. «*La reivindicación 24 se caracteriza porque la composición se formula como una forma de dosificación unitaria individual. Esto no se considera un elemento técnico esencial de una formulación y está relacionado con un método de tratamiento de dosis unitaria. Se requiere a la solicitante para que caracterice la composición mediante sus elementos esenciales como se indicó anteriormente.*»

En respuesta a lo anterior, me permito indicar que, tal y como se expuso en el numeral 1 del presente memorial, la reivindicación 24 fue restringida usando la materia de la reivindicación 25 anteriormente presentada. Por tanto, la objeción a este respecto se ve superada.

En consecuencia, me permito manifestar que el nuevo capítulo reivindicatorio adjunto al presente memorial, que incluye 24 reivindicaciones, cumple a cabalidad con las disposiciones del Artículo 30 de la Decisión 486/00.

4. <u>Descripción</u>

Por otro lado, en cuanto a lo señalado por el examinador sobre que: «*La composición reclamada carece de sustento descriptivo toda vez que la solicitud adolece de ejemplos de formulaciones, métodos de elaboración de las mismas y de ensayos relacionados con la valoración de formulaciones específicas que hayan permitido resolver algún problema técnico*», me permito señalar, además de lo mencionado en el numeral 3.1 del presente memorial, que no es necesario especificar excipientes que puedan usarse para obtener la composición reivindicada, toda vez que una persona normalmente versada en la materia, teniendo como objetivo diseñar una composición farmacéutica adecuada del Compuesto A, sería capaz de seleccionarlos fácilmente junto con sus cantidades. Lo único necesario para que dicha persona pueda diseñarla es conocer el principio activo y su cantidad dentro de la formulación, lo cual se describe claramente en las reivindicaciones y la descripción de la solicitud en estudio.

Asimismo, me permito dirigir su atención a la sección de la descripción de la presente solicitud que va desde la línea 21 de la página 19 a la línea 14 de la página 20, en particular en donde se menciona que: «*Una persona de experiencia ordinaria en la técnica*

puede seleccionar uno o más de los excipientes mencionados en lo anterior con respecto a las propiedades deseadas particulares de la forma de dosificación oral granulada y/o sólida mediante experimentación de rutina y sin ninguna carga indebida.» Por tanto, me permito solicitar a ese Despacho que la objeción a este respecto sea retirada, toda vez que la composición reclamada sí encuentra suficiente soporte en la memoria descriptiva de la presente solicitud.

5. <u>Nivel inventivo</u>

Finalmente, el examinador establece en su concepto técnico la falta de nivel inventivo de la presente solicitud en vista de las enseñanzas descritas en los documentos EP1730152 (D1) y "Guideline for Industry. Dose-Response Information to Support Drug Registration. ICH-E4, FDA, 1994" (D2).

No obstante, me permito dirigir su atención al artículo científico adjunto sobre el resultado de TA-8995 (que es el Compuesto A) en su estudio de fase 2 en pacientes con dislipidemia leve (estudio TULIP) solo y en combinación con estatinas (Hovingh, G. K., *et al.* "Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial", *Lancet* 2015; 386:452–60). En este estudio, se reportó que:

> "Muchos pacientes no alcanzan niveles óptimos de colesterol LDL a pesar de una dosis máxima tolerada de estatinas. Se garantiza una disminución adicional del colesterol LDL en estos individuos y la inhibición de CETP causa tal efecto. Nuestros hallazgos muestran que TA-8995, un nuevo inhibidor de CETP, tiene un efecto beneficioso sobre los lípidos y lipoproteínas; El colesterol LDL disminuyó en un 45·3% y los niveles de apoB en un 33·7%, mientras que las concentraciones de colesterol HDL aumentaron hasta un 179·1% y la apoA-I en un 63·4%. Por último, la capacidad de eflujo de colesterol aumentó en un 36·7% en pacientes asignados aleatoriamente a 10 mg de TA-8995. Todos estos efectos fueron similares en pacientes en monoterapia o en combinación con una estatina. No se informaron eventos adversos serios relacionados y el medicamento fue bien tolerado. Estos hallazgos son importantes porque proporcionan a los médicos la evidencia de que la inhibición de CETP con TA-8995 es una reducción efectiva del colesterol LDL y un tratamiento que aumenta el colesterol HDL con el objetivo de prevenir la enfermedad

> cardiovascular." (*véase* la página 459 del artículo, parte superior de la página, bajo el título "Panel: Research in context")

V*éase* también la página 460 de dicho artículo, primer párrafo completo, que muestra que la dosis sorprendentemente baja de TA 8995 (Compuesto A) se elimina rápidamente en el tejido adiposo, lo que es una ventaja adicional en comparación con el otro inhibidor conocido de CETP que ha estado en los estudios clínicos con dosis altas (Anacetrapib: 100 mg diarios).

> "Los inhibidores de CETP son lipofílicos por naturaleza y se ha informado recientemente que el anacetrapib se retiene en el tejido adiposo y puede permanecer detectable en el suero años después de la interrupción de la dosificación. Por el contrario, TA-8995 no se retiene en el tejido adiposo y se elimina rápidamente después de la interrupción de la dosificación. Además, no se detectó TA-8995 en tejido adiposo o hepático después de 9 meses de dosificación crónica de monos cynomolgus a una dosis supraterapéutica (datos no mostrados)."

Véase también el artículo científico adjunto: REVEAL Collaborative Group, *et al.* "Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL)—A large-scale, randomized, placebo-controlled trial of the clinical effects of anacetrapib among people with established vascular disease: Trial design, recruitment, and baseline characteristics", *Am Heart J* 2017; 187:182-90, específicamente en la página 189, segundo párrafo completo, bajo el título "Discussion", en donde se muestra que la baja dosificación del inhibidor de CETP, que es de naturaleza lipofílica, sigue siendo una necesidad insatisfecha.

> "El seguimiento prolongado de un subconjunto de participantes de DEFINE mostró que el anacetrapib tiene un largo plazo en una vida media tal que los niveles bajos de anacetrapib (alrededor del 8% de las exposiciones mínimas durante el tratamiento en estado estacionario aparente y el 2% de concentraciones máximas aparentes en estado estacionario) se detectaron en sangre de 2.5 a 4 años después del cese de la terapia."

Por otro lado, me permito reiterar que el documento WO 2005/095409 enseña una amplia gama general de dosificación de una clase de compuestos derivados de tetrahidroquinolina en la unidad de mg/kg/día, de la siguiente manera:

> "La dosis de un compuesto (I) de la presente invención o una sal farmacéuticamente aceptable del mismo varía dependiendo de la ruta de administración, la edad, el peso corporal, la enfermedad y el estado/severidad del paciente. Sin embargo, normalmente puede estar en el intervalo de aproximadamente 0.001 a 1.000 mg/kg/día, preferiblemente en el intervalo de aproximadamente 0.01 a 100 mg/kg/día, más preferiblemente en el intervalo de aproximadamente 0.1 a 10 mg/kg/día."

Por lo tanto, basándose en las enseñanzas de WO 2005/095409, los expertos en la técnica estarían motivados a creer que la dosificación para dar a un hombre caucásico promedio de 198 lb, que se calcula que es un hombre de aproximadamente 90 kg, dentro de los rangos de dosis descritos anteriormente en las unidades de mg/kg/día enseñadas por el documento WO 2005/095409 estarían entre 0.9 mg y 90.000 mg por día, preferiblemente en el intervalo de aproximadamente 0.9 mg a 900 mg por día, más preferiblemente en el intervalo de aproximadamente 9 mg a 90 mg por día, respectivamente, el cual es un rango muy amplio. Junto con las dosis diarias de más de 60 mg conocidas para otros inhibidores de CETP en ensayos clínicos como se describe en el artículo de Lancet (Torcetrapib: 60 mg al día, Dalcetrapib: 600 mg al día, Evacetrapib: 130 mg al día y Anacetrapib: 100 mg al día) los expertos en la técnica estarían motivados a creer que la dosificación efectiva para el Compuesto A sería de al menos 60 mg o más. O, alternativamente, con base en el intervalo más preferido de WO 2005/095409 de 9 mg a 90 mg de dosis diaria, los expertos en la técnica habrían estado motivados a escoger los 90 mg, que es mucho más cercano a la dosis de 60 mg a 100 mg como ha sido la dosis normal para los otros tres inhibidores anteriores de CETP en ensayos clínicos, en comparación con la dosis más baja de 9 mg. Por lo tanto, con base en el documento WO 2005/095409, sin retrospectiva, los expertos en la técnica no habrían estado motivados a formular una composición que comprendiera desde 1 mg, 2.5 mg, 5 mg, 10 mg o 25 mg por día de Compuesto A sin experimentación adicional.

Además, como se presentó anteriormente, se encontró que la dosis diaria de 130 mg de Evacetrapib no era efectiva, *véase* el informe de ensayo clínico adjunto. De nuevo, esto motivaría aún más a la persona normalmente versada en la materia a elegir una dosis más alta para el Compuesto A, lo que demuestra que la dosis baja está lejos de ser obvia.

En consecuencia, me permito señalar que los documentos D1 y D2 no afectan el nivel inventivo de la presente solicitud y la objeción a este respecto se ve superada, toda vez que no existe motivación alguna para que una persona del oficio normalmente versada en la materia derive de manera obvia la presente invención a partir de dichas anterioridades, demostrándose así que las reivindicaciones 1 a 24 del nuevo capítulo reivindicatorio cumplen con el requisito de nivel inventivo según los lineamientos del Artículo 18 de la Decisión 486/00.

6. <u>Conclusión</u>

Finalmente, a la luz de las modificaciones al capítulo reivindicatorio y los argumentos presentados, es posible concluir lo siguiente:

6.1. La presente solicitud es clara, concisa y está debidamente soportada por la descripción, cumpliendo así con los requerimientos del Artículo 30 de la Decisión 486/00.

6.2. La presente solicitud es patentable sobre los documentos D1 y D2, de acuerdo con los requerimientos del Artículo 18 de la Decisión 486/00.

Por tanto, atentamente me permito solicitar a ese Despacho otorgar el privilegio de patente solicitado a la solicitud en estudio, toda vez que cumple a cabalidad con los requerimientos de la Decisión 486/00.

7. Anexos

7.1. Nuevo capítulo reivindicatorio que comprende 24 reivindicaciones.

7.2. Artículo científico: Hovingh, G. K., *et al.* "Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial", *Lancet* 2015; 386:452–60.

7.3. Artículo científico: REVEAL Collaborative Group, *et al.* "Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL)—A large-scale, randomized, placebo-controlled trial of the clinical effects of anacetrapib among people with established vascular disease: Trial design, recruitment, and baseline characteristics", *Am Heart J* 2017; 187:182-90.

7.4. Informe de ensayo clínico del Evacetrapib.

7.5. Comprobante de pago de tasa para nuevo examen de patentabilidad.

Señor Director,

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Nuevo capítulo reivindicatorio
Septiembre 20, 2018

REIVINDICACIONES

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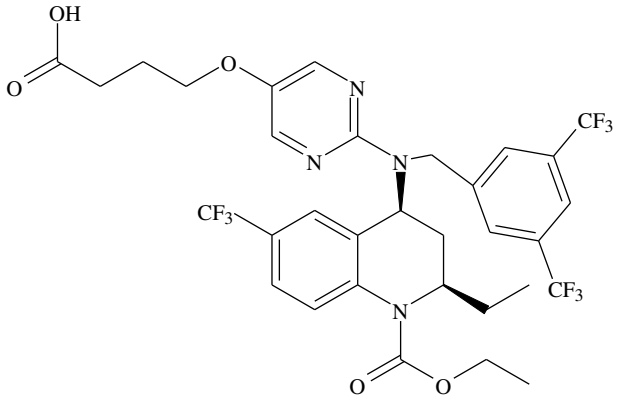

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Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial

G Kees Hovingh, John J P Kastelein, Sander J H van Deventer, Patrick Round, John Ford, Danish Saleheen, Daniel J Rader, H Bryan Brewer, Philip J Barter

Lancet 2015; 386: 452–60

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See Online/Comment http://dx.doi.org/10.1016/S0140-6736(15)60608-0

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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.

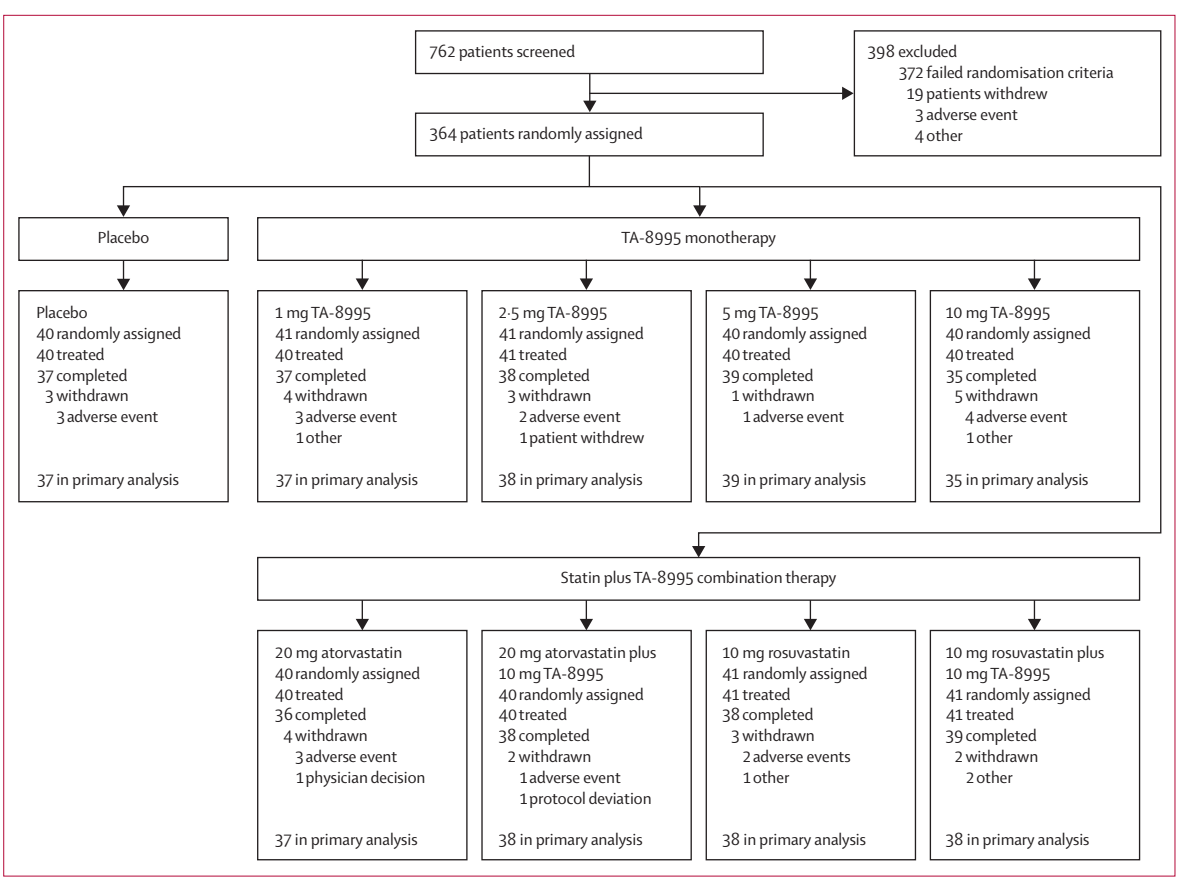

Figure 1: **Trial profile**

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

See Online for appendix

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.

	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**

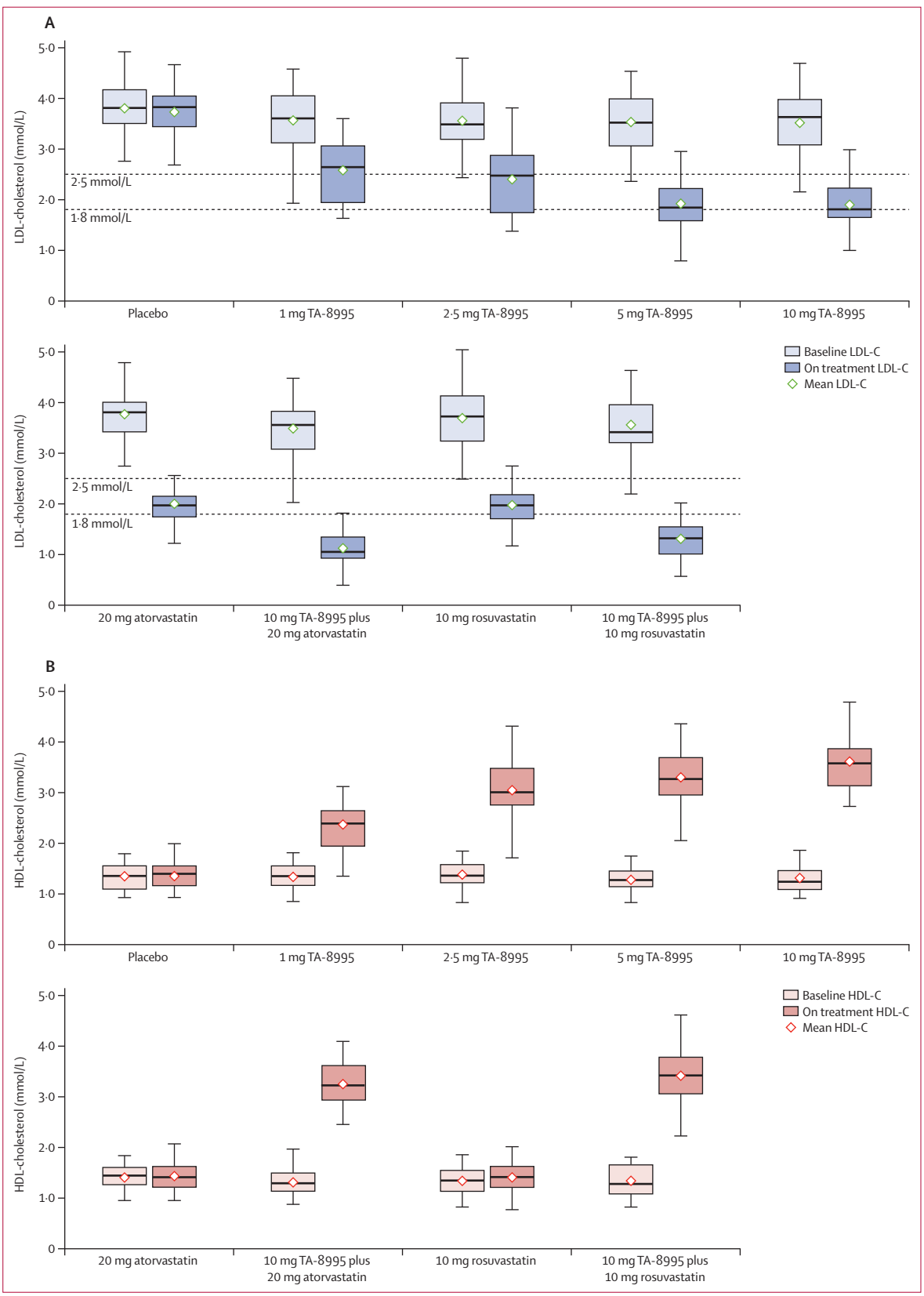

Figure 2: **Baseline and week 12 data for LDL (A) and HDL (B)**
Boxes show the 25th and 75th percentiles, whiskers show the minimum and maximum values, horizontal lines show the median, and green circles show the mean. The data only include patients who had both baseline and week 12 data. The changes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

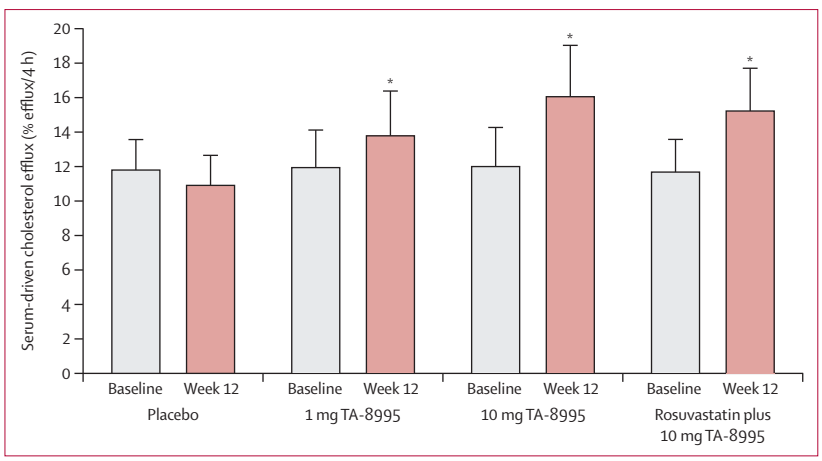

Figure 3: **Baseline and week 12 data for serum-driven cholesterol efflux**
Bars are means and error bars are standard deviations. The baseline data only include patients who had both baseline and week 12 data. The changes from baseline for all active treatments showed significant differences from placebo 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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Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL)—A large-scale, randomized, placebo-controlled trial of the clinical effects of anacetrapib among people with established vascular disease: Trial design, recruitment, and baseline characteristics

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Background Patients with prior vascular disease remain at high risk for cardiovascular events despite intensive statin–based treatment. Inhibition of cholesteryl ester transfer protein by anacetrapib reduces low-density lipoprotein (LDL) cholesterol by around 25% to 40% and more than doubles high-density lipoprotein (HDL) cholesterol. However, it is not known if these apparently favorable lipid changes translate into reductions in cardiovascular events.

Methods The REVEAL study is a randomized, double-blind, placebo-controlled clinical trial that is assessing the efficacy and safety of adding anacetrapib to effective LDL-lowering treatment with atorvastatin for an average of at least 4 years among patients with preexisting atherosclerotic vascular disease. The primary assessment is an intention-to-treat comparison among all randomized participants of the effects of allocation to anacetrapib on major coronary events (defined as the occurrence of coronary death, myocardial infarction, or coronary revascularization).

Results Between August 2011 and October 2013, 30,449 individuals in Europe, North America, and China were randomized to receive anacetrapib 100 mg daily or matching placebo. Mean (SD) age was 67 (8) years, 84% were male, 88% had a history of coronary heart disease, 22% had cerebrovascular disease, and 37% had diabetes mellitus. At the randomization visit (after at least 8 weeks on a protocol-defined atorvastatin regimen), mean plasma LDL cholesterol was 61 (15) mg/dL and HDL cholesterol was 40 (10) mg/dL.

Interpretation The REVEAL trial will provide a robust evaluation of the clinical efficacy and safety of adding anacetrapib to an effective statin regimen. Results are anticipated in 2017. (Am Heart J 2017;187:182-90.)

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Background

Large-scale randomized trials have shown that lowering low-density lipoprotein (LDL) cholesterol concentration by about 40 mg/dL (1 mmol/L) for 4 to 5 years reduces the risk of coronary events (including myocardial infarction [MI], coronary death, and revascularization procedures) and stroke by about one-fifth,[1] and that lowering LDL cholesterol more (either with more effective statin regimens or with the addition of ezetimibe) produces further reductions in risk.[2,3] Nevertheless, among individuals who already have occlusive vascular disease, the risk of cardiovascular events remains high.[2,3]

Although higher high-density lipoprotein (HDL) cholesterol concentration is associated with lower risk of coronary

events in observational epidemiologic studies,[4,5] there is little evidence that treatments that raise HDL cholesterol reduce the risk of vascular events. Trials using fibrates (which raise HDL cholesterol by about 5%-10%) have produced mixed results,[6] whereas adding niacin (which increases HDL cholesterol by 14%-20%) to a statin had no effect on the risk of cardiovascular events but was associated with significant hazards (including serious adverse events [SAEs] related to the gastrointestinal and musculoskeletal systems, skin, diabetes, infection, and bleeding).[7,8]

Cholesteryl ester transfer protein (CETP) facilitates exchange of cholesteryl esters and triglycerides between HDL particles and atherogenic apolipoprotein B–containing particles in the plasma. Genetic variants that lead to lower CETP activity are associated with higher HDL cholesterol levels and lower risk of coronary heart disease[9,10] (by contrast with other genetic variants that impact HDL cholesterol levels).[11] Pharmacological CETP inhibition produces increases in HDL cholesterol and apolipoprotein A1, along with reductions in LDL cholesterol and apolipoprotein B.[12] The magnitude of these effects varies between different CETP inhibitors. Torcetrapib was the first CETP inhibitor to be studied in a large-scale outcome trial. However, the ILLUMINATE trial in 15,000 patients with preexisting cardiovascular disease was stopped prematurely in 2007 because of an excess risk of death among patients allocated to receive torcetrapib.[13] Torcetrapib was found to increase systolic blood pressure by about 5 mm Hg as well as causing increases in blood sodium, bicarbonate, and aldosterone concentrations.[13-15]

Cardiovascular outcome trials with 2 other CETP inhibitors were also terminated early because of a lack of efficacy. In 2012, the Dal-OUTCOMES trial of dalcetrapib in 16,000 patients with a recent acute coronary syndrome was stopped prematurely because of a lack of clinically meaningful reductions in cardiovascular events but with no significant safety concerns.[16] Dalcetrapib has only modest effects on blood lipids, increasing HDL cholesterol by about 30% with no effect on LDL cholesterol, and also increasing systolic blood pressure by 0.6 mm Hg in Dal-OUTCOMES. In 2015, the ACCELERATE trial of evacetrapib, which doubles HDL cholesterol and lowers LDL cholesterol by about one quarter,[17,18] was stopped early because of insufficient evidence of efficacy.[19,20] There was an increased risk of investigator-reported hypertension and a 1 mm Hg increase in systolic blood pressure.

Anacetrapib is an orally active CETP inhibitor that was well tolerated in early-phase studies. In the placebo-controlled DEFINE trial among 1,600 patients followed up for 18 months, anacetrapib 100 mg daily produced substantial increases in HDL cholesterol and apolipoprotein A1 (138% and 45%, respectively) and reductions in LDL cholesterol, apolipoprotein B, and lipoprotein(a) (40%, 21%, and 36%, respectively).[21] However, subsequent investigations suggest that the reduction in LDL cholesterol may be somewhat smaller (around 25%) if measured by β-quantification rather than direct methods.[22] There have been no discernible effects on resting or ambulatory blood pressure or on plasma aldosterone concentrations.[23]

The REVEAL trial was designed to assess the clinical efficacy and safety of anacetrapib 100 mg once daily among patients with preexisting atherosclerotic vascular disease who are also receiving effective LDL-lowering therapy using atorvastatin. In this article, we present the REVEAL trial design, prerandomization recruitment and run-in period, baseline participant characteristics, and data analysis plan.

Methods

Aims

The REVEAL trial aimed to randomize at least 30,000 participants 50 years or older with preexisting atherosclerotic vascular disease between anacetrapib 100 mg daily and matching placebo for a median of at least 4 years (Supplementary Figure 1). All participants were to receive effective LDL-lowering treatment using atorvastatin. The primary outcome for the assessment of efficacy is *major coronary event*, which is defined as coronary death, MI, or coronary revascularization (Figure 1).

Study organization

The study was designed by the independent investigators at the Clinical Trial Service Unit at the University of Oxford (the regulatory trial sponsor) in collaboration with the TIMI Study Group based at Brigham and Women's Hospital, Boston, and Merck & Co, Inc (Merck), which manufactures anacetrapib and provides funding for the study. The independent Steering Committee is responsible for drafting the main reports from the study. Although Merck has the opportunity to comment on drafts of manuscripts, it otherwise has no role in the analysis of the data presented, the preparation and approval of this manuscript, or the decision to submit it for publication. The study protocol (see Supplementary Material) was approved by the relevant institutional review board and drug regulatory authority for each participating center.

Eligibility

The REVEAL trial aimed to enroll a broad range of participants at high risk for future cardiovascular events (see Figure 2). Men and women older than 50 years were considered eligible if they met at least one of the inclusion criteria (history of MI, cerebrovascular atherosclerotic disease, peripheral arterial disease, or diabetes mellitus with other evidence of symptomatic coronary heart disease), had none of the exclusion criteria, and if their own doctor did not consider there to be a definite contraindication to either anacetrapib or atorvastatin (the protocol-specified background statin treatment for all participants).

Figure 1

Primary outcome

Major coronary event: Coronary death*, myocardial infarction or coronary revascularization procedure

Secondary outcomes†

Major atherosclerotic event: Coronary death, myocardial infarction or presumed ischaemic stroke (the key secondary outcome)

Presumed ischaemic stroke: (i.e. not known to be haemorrhagic)

Major vascular event: Coronary death, myocardial infarction, coronary revascularization procedure or presumed ischaemic stroke

* Coronary death includes deaths due to myocardial infarction, other consequences of coronary atherosclerosis (such as ischaemic heart failure) and sudden cardiac death. Definitions of each of these outcomes are provided in the Supplementary Material.

† In addition, each of the individual components of the primary outcome will be tested separately. Further details of all analyses are provided in the Data Analysis Plan (see Supplementary Material).

Primary and secondary outcomes.

Invitation, screening, and run-in phase

Extensive prescreening efforts were made to identify large numbers of potential participants at each recruiting site. Potentially eligible patients were identified from clinical records (including electronic health care records) and, in many places, were contacted to seek their provisional agreement to attend a screening visit. The exact methods varied by center and by country, and in all cases were subject to appropriate institutional review board approval and compliance with data privacy regulations. Potential participants were given information about the study and invited to attend a screening visit.

At the screening visit, relevant medical history, current medication, and other factors pertinent to eligibility were recorded directly on to the screening visit form on the study IT system (which was designed to ensure that complete information was obtained and to prompt actions in line with the protocol). Potentially eligible individuals had the study explained to them by the clinic staff and were asked to provide written informed consent. In addition, they were asked to indicate on the consent form which, if any, of the samples of plasma, serum, cells, or urine could be stored long term for future unspecified research analyses. Blood pressure was measured and a non–fasting blood sample was taken for immediate measurement of total cholesterol, alanine transaminase (ALT), creatine kinase (CK), and creatinine using a Reflotron Plus (Roche Diagnostics International, Rotkreuz, Switzerland) dry chemistry analyzer. These results were recorded directly on the study clinic IT system, which provided an assessment of eligibility and determined the atorvastatin dose to be used for that individual (see below). At the end of the screening visit, eligible participants were issued with a 12-week supply of active atorvastatin (at an appropriate dose) and placebo anacetrapib, with 1 tablet of each to be taken daily. All other lipid-modifying treatments were stopped. An appointment was made for a randomization visit in 8 to 12 weeks.

The prerandomization, single-blind, run-in phase was intended to help identify and exclude before randomization those individuals who would be unlikely to comply with long-term study treatment and follow-up. During run-in, the local investigator (and, where appropriate, each individual's primary care physician or hospital specialist) was given a description of their patient's medical history, previous lipid-modifying treatment and screening visit total cholesterol result, and advised of the atorvastatin dose that would be provided during the trial. The doctor was asked to indicate whether, in their view, their patient was unsuitable for entry into the randomized phase of the study (for whatever reason). The run-in period also provided screened participants with the opportunity to consider whether they remained willing to take part in the randomized comparison, take study medication, and attend follow-up visits for at least 4 to 5 years.

Determination of atorvastatin dose

All participants who entered the run-in phase were issued with an atorvastatin regimen that was intended to reduce their LDL cholesterol to less than 77 mg/dL (2 mmol/L) and which was at least as intensive as their current LDL-lowering treatment (see Supplementary Material). At the screening visit, a computerized algorithm used the dry chemistry total cholesterol measurement and the type and dose of their current (prestudy) LDL-lowering therapy (statin and/or ezetimibe) to determine eligibility and the minimum dose of study atorvastatin (either 10 or 20 mg in China, 20 or 80 mg in other countries) likely to be required to lower total cholesterol to less than 135 mg/dL (3.5 mmol/L). Individuals were excluded if they were already receiving LDL-lowering treatment that was more intensive than the maximum

Figure 2

Inclusion criteria

Patients must be aged at least 50 at the time of initial invitation, and at least one of the following inclusion criteria must be satisfied:

- History of myocardial infarction (MI);
- Cerebrovascular atherosclerotic disease (history of presumed ischaemic stroke or carotid revascularization);
- Peripheral arterial disease (history of non-coronary revascularization, including aortic aneurysm repair or graft); or
- Diabetes mellitus with other evidence of symptomatic coronary heart disease (treatment or hospitalization for angina, or a history of coronary revascularization or acute coronary syndrome).

Exclusion criteria

- Acute MI, acute coronary syndrome or stroke within 4 weeks prior to Screening Visit or during run-in;
- Planned coronary revascularization procedure within the next 6 months;
- Definite history of chronic liver disease, or abnormal liver function (i.e. ALT >2x ULN)*;
- Severe renal insufficiency (i.e. creatinine >2.3 mg/dL [200 μmol/L], dialysis or functioning renal transplant);
- Evidence of active inflammatory muscle disease, or CK >3x ULN;
- Previous significant adverse reaction to a statin or anacetrapib;
- Current treatment with any of the following lipid-lowering treatments:
  - (i) a regimen considered to produce substantially greater LDL cholesterol reduction than atorvastatin 20 mg daily for individuals in China or 80 mg daily for those in other countries;
  - (ii) fibric acid derivative ("fibrate", including gemfibrozil); or
  - (iii) niacin (nicotinic acid) at doses above 100 mg daily;
- Concurrent treatment with a medication that is contraindicated with anacetrapib or atorvastatin†;
- Known to be poorly compliant with clinic visits or prescribed medication;
- Medical history that might limit the individual's ability to take trial treatments for the duration of the study;
- Women of child-bearing potential (unless using adequate contraception); or
- Current participation in a clinical trial with an unlicensed drug or device.

Individuals were also to be excluded at the Screening visit if it was considered unlikely that they would achieve total cholesterol <135 mg/dL (3.5 mmol/L) on the highest atorvastatin dose available in their region‡.

Additional exclusion criteria at the randomization visit§

In addition to the above, individuals must be excluded at the randomization visit if any of the following are true:

- Total cholesterol above 155 mg/dL (4 mmol/L)
- Non-compliant with run-in treatment (<90% scheduled run-in medication taken)‖
- Individual is no longer willing to be randomized into the 4-5 year trial
- The individual's doctor is of the view that their patient should not be randomized

ALT – alanine transaminase; CK – creatine kinase; LDL – low density lipoprotein; ULN – upper limit of normal
* Individuals with a history of acute hepatitis are eligible provided this ALT limit is not exceeded
† Individuals who were taking such drugs temporarily could be re-screened when they discontinue them, if considered appropriate.
‡ atorvastatin 20 mg daily in China or 80 mg daily in other countries
§ The randomization visit occurred after an 8-12 weeks run-in period during which participants received study atorvastatin plus placebo anacetrapib
‖ Tablet counts were not required

Inclusion and exclusion criteria for entry into the REVEAL trial.

atorvastatin dose available in the trial or if it was unlikely that they would achieve the target total cholesterol on that dose of atorvastatin.

Randomization visit

At the randomization visit, eligibility was rechecked and information on SAEs and any other significant problems during the run-in period were recorded. Nonstudy medication, compliance with run-in treatment, and consent information were checked. Information about smoking history and alcohol intake was sought and an assessment of quality of life was made using the EQ5D questionnaire. Blood pressure (measured once with patient sitting using Omron BP760 (Omron Healthcare UK, Milton Keynes, UK) or equivalent local model), height, weight, and hip, waist, and neck circumference were measured. All details were recorded directly on the Randomization Form on the clinic IT system. A blood sample was taken for immediate dry chemistry measurement of total cholesterol, ALT, and CK. Individuals could only remain eligible if total cholesterol was ≤155 mg/dL (4 mmol/L), ALT ≤2× upper limit of normal, and CK ≤3× upper limit of normal. Additional non–fasting blood samples and a urine sample were taken for central laboratory assays of lipid profile, glycosylated hemoglobin, plasma creatinine, and urinary albumin/creatinine ratio (see Supplementary Material). Samples of genetic material,

plasma, serum, and urine are being stored long term for future analysis, subject to appropriate consents.

Eligible and consenting individuals were allocated anacetrapib or placebo using a minimized randomization program embedded within the clinic IT system that helps maximize balance between the treatment groups with respect to prognostically important variables (see Supplementary Material).[24] Randomized participants were issued with a 7-month supply of study treatment consisting of (*a*) anacetrapib 100 mg or matching placebo, and (*b*) active atorvastatin (at the same dose issued at the screening visit). An appointment for the first postrandomization follow-up visit was made and the participant's doctor(s) was notified that his/her patient had been randomized.

Post-randomization follow-up

After randomization, it is intended that all participants remain on study treatment and that follow-up information is collected for the full duration of the study. Clinic follow-up visits are scheduled at 2 and 6 months initially (with an additional visit at 4 months in China, at the request of the Chinese Food and Drug Administration), and then 6 monthly until the end of the study. Additional "early recall" visits are arranged for any participants who require review outside their planned visit schedule. Details of the follow-up visit assessments are provided in the Supplementary Material. Wherever possible, extended follow-up (off study treatment) of all surviving randomized participants will continue for at least 2 years beyond the final study visit to provide information on the longer-term safety and efficacy of anacetrapib.

Adverse event recording and adjudication of potential study outcomes

At each follow-up visit, study staff seek details of all SAEs (including study outcomes and reasons for hospitalization), any non-serious adverse events attributed to or resulting in discontinuation of study treatment, and any symptoms of muscle pain or weakness or suggestive of hepatitis (loss of appetite, nausea, jaundice, lethargy, or malaise). At the request of the US Food and Drug Administration, information on all other non-serious adverse events is sought for participants in North America. Potential study outcomes are adjudicated by clinicians based at or overseen by the Central Coordinating Office, blind to study treatment allocation or blood lipid values and using standard definitions (see Supplementary Material).

Statistical considerations

Sample size and predicted number of events. Based on a major coronary event rate of 1.8% per annum and median follow-up of 4 years, a trial of 30,000 participants would have 88% power at 2-tailed $P < .01$ to detect a 15% relative risk reduction (see Supplementary Material). Follow-up of all randomized participants is planned to continue for a median of at least 4 years, and until at least 1900 participants have had an unrefuted major coronary event (primary end point) plus at least 950 participants have had a coronary death or MI.

Data analysis plan. All participants randomized to anacetrapib will be compared with all participants randomized to placebo, regardless of whether a participant received all, some or none of the allocated treatment (ie, intention-to-treat analyses). For each outcome, survival analytic methods will be used to evaluate the time to the first event during the entire study period. The log-rank method will be used to estimate the average event rate ratio comparing all those allocated active anacetrapib with all those allocated placebo. A 2-tailed P value <.05 will be considered statistically significant. Further details (including the approach to control for multiplicity) are provided in the protocol, Data Analysis Plan, and other online Supplementary Material, which were finalized by the trial Steering Committee blind to any information on the effect of study treatment on study outcomes.

Role of the independent Data Monitoring Committee. An independent Data Monitoring Committee (DMC) is responsible for reviewing interim unblinded analyses of the effect of randomized treatment allocation on all SAEs and other study outcomes. The DMC is to advise the Steering Committee if, in their view, any modification to the protocol is required. Such assessments are carried out at a frequency relevant to the stage of the study (typically at 6-12 monthly intervals with a Chairman's review every 3-6 months). Further details, including guidelines for once only consideration of stopping for benefit or futility at 3 years' median follow-up, are provided in the DMC Charter (see Supplementary Material).

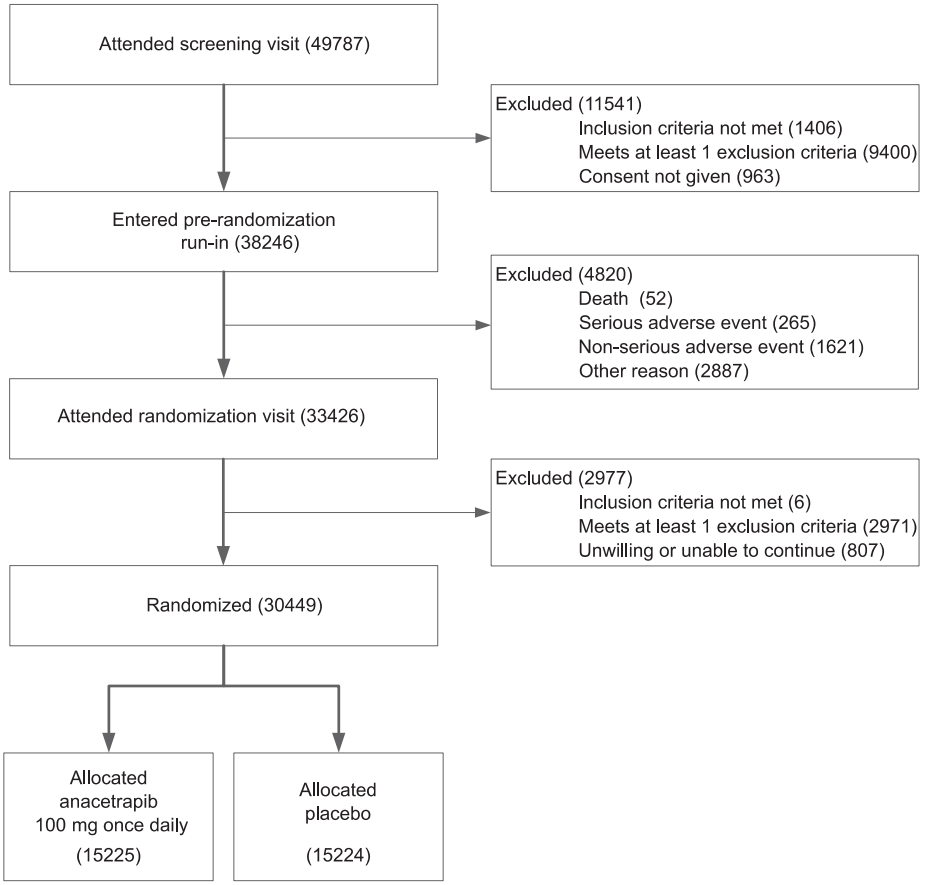
Results

Screening and run-in

A total of 49,787 patients attended a screening visit (see Figure 3): 29,318 in Europe, 8,249 in North America, and 12,220 in China (see Supplementary Table I). Data from one additional site in the United States have been excluded from this report because of evidence of significant breaches of Good Clinical Practice and the study protocol (see Supplementary Material).

Of the 49,787 people screened, 11,541 (23.2%) were excluded at the screening visit, 4,820 (9.7%) withdrew during the run-in period, and 2,977 (6.0%) were not eligible at the randomization visit. Of those screened, 1,406 (2.8%) did not meet any of the inclusion criteria, 1,441 (2.9%) were excluded on the basis of medical history, 1,392 (2.8%) were excluded because of concerns about long-term compliance with study medication and/or attendance at clinic visits, and 963 (1.9%) did not give consent (see Supplementary Table II). A total of 1,550 (3.1%) were excluded on the basis of medication history, with the chief reasons being a participant report of previous adverse reaction to a statin (735 [1.5%]) and the use of an LDL-lowering treatment regimen (statin and/or

Figure 3



Note: Participants may have more than 1 reason for not progressing from one stage of the process to the next.

Trial profile — flow of participants through the REVEAL trial.

ezetimibe) that was considered to be more potent than the maximum dose of study atorvastatin (621 [1.2%]). A total of 5,437 (10.9%) individuals were excluded on the basis of their blood assay results, with 4,814 (9.7%) being due to a total cholesterol result that, together with knowledge of their current LDL-lowering treatment, gave a predicted total cholesterol result that was unlikely to be less than 135 mg/dL (3.5 mmol/L) on the maximum dose of study atorvastatin for their region. Overall, of the 11,541 individuals who were excluded at the screening visit, 5,435 (47%) were excluded either because their current LDL-lowering treatment was considered to be more potent than the maximal dose of study atorvastatin available or because it was considered unlikely that their total cholesterol would be less than 135 mg/dL (3.5 mmol/L) on study atorvastatin.

Of the 38,246 individuals who entered the run-in phase, 4,820 (12.6%) withdrew before attending a randomization visit (see Supplementary Table III). A total of 52 (0.1%) died of causes unrelated to study medication, 265 (0.7%) withdrew because of a nonfatal SAE (of which 4 were believed to be caused by the study atorvastatin), and 1,621 (4.2%) withdrew because of a non-serious adverse event (with musculoskeletal and gastrointestinal disorders being the most common). A total of 2887 (7.5%) had other reasons for withdrawing from run-in, principally concerns about or difficulty taking tablets, difficulty in traveling or attending clinic, or advice from their doctor.

Of the 33,426 individuals who attended a randomization visit, 2,977 (8.9%) were not eligible for randomization (see Supplementary Table IV). Of these, 6 (0.0%) no longer met the inclusion criteria, 1,063 (3.2%) were excluded on the basis of medical history (including 1 reported serious adverse reaction to study atorvastatin), 448 (1.3%) were on a contraindicated medication or poorly compliant with the run-in treatment (atorvastatin plus placebo anacetrapib), there were concerns about long-term compliance with study medication in 580

Table. Baseline characteristics of randomized participants.

	Europe	North America	China	Total
Number randomized	15,738	6082	8629	30,449
Age (y)	68 ± 8	67 ± 8	64 ± 8	67 ± 8
Male	13,652 (87%)	5058 (83%)	6824 (79%)	25,534 (84%)
Atorvastatin dose*				
Low	7969 (51%)	2621 (43%)	4519 (52%)	15,109 (50%)
High	7769 (49%)	3461 (57%)	4110 (48%)	15,340 (50%)
Prior disease†				
Coronary heart disease	13,306 (85%)	5697 (94%)	7676 (89%)	26,679 (88%)
Cerebrovascular disease	3348 (21%)	1131 (19%)	2302 (27%)	6781 (22%)
Peripheral arterial disease	1645 (10%)	714 (12%)	76 (1%)	2435 (8%)
Diabetes	4678 (30%)	2682 (44%)	3960 (46%)	11,320 (37%)
Heart failure	785 (5%)	343 (6%)	643 (7%)	1771 (6%)
<12 mo since qualifying event	2420 (15%)	1060 (17%)	1933 (22%)	5413 (18%)
Physical measurements				
Systolic blood pressure (mm Hg)	131 ± 18	129 ± 18	133 ± 20	131 ± 19
Diastolic blood pressure (mm Hg)	78 ± 11	76 ± 11	79 ± 12	78 ± 11
Body mass index (kg/m^2)	29 ± 5	31 ± 6	26 ± 3	29 ± 5
Waist-hip ratio‡	0.97 ± 0.08	0.98 ± 0.08	0.92 ± 0.05	0.96 ± 0.07
Medication				
ACE inhibitor or ARB	11,879 (75%)	4400 (72%)	4050 (47%)	20,329 (67%)
Antiplatelet therapy	14,261 (91%)	5654 (93%)	7992 (93%)	27,907 (92%)
Diuretic	3965 (25%)	1831 (30%)	728 (8%)	6524 (21%)
Calcium-channel blocker	4045 (26%)	1461 (24%)	2679 (31%)	8185 (27%)
β-Blocker	10,897 (69%)	4665 (77%)	5112 (59%)	20,674 (68%)
Biochemistry				
Total cholesterol (mg/dL)	136 ± 21	126 ± 21	129 ± 22	132 ± 21
LDL cholesterol (mg/dL)	63 ± 15	58 ± 14	59 ± 15	61 ± 15
HDL cholesterol (mg/dL)	43 ± 10	37 ± 9	37 ± 8	40 ± 10
Non–HDL cholesterol (mg/dL)	93 ± 19	89 ± 19	91 ± 20	92 ± 19
Triglycerides (mg/dL)	119 (87-167)	122 (87-172)	135 (97-192)	124 (89-174)
Apolipoprotein A1 (mg/dL)	124 ± 19	115 ± 18	116 ± 15	120 ± 18
Apolipoprotein B (mg/dL)	67 ± 13	64 ± 12	61 ± 12	65 ± 13
Lipoprotein(a) (nmol/L)	22 (8-104)	26 (9-111)	22 (10-61)	23 (9-88)
Glomerular filtration rate (ml/min per 1.73 m^2)‡	81 ± 17	80 ± 18	90 ± 15	83 ± 17
Urinary albumin/creatinine ratio (mg/g)	8 (4-21)	8 (4-29)	8 (4-23)	8 (4-23)

Results are count (%), mean ± SD, or median (interquartile range).
Abbreviations: *ACE*, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker.
* Low-dose atorvastatin = 10 mg in China and 20 mg elsewhere; high-dose atorvastatin = 20 mg in China and 80 mg elsewhere.
† Participants may have a history of more than 1 of these conditions.
‡ Estimated using the CKD EPI formula.[30]

(1.7%), and 807 (2.4%) were unwilling or unable to attend regular study visits. A total of 1,606 (4.8%) individuals were excluded on the basis of the blood results, including 1,097 (3.3%) with a total cholesterol result greater than 155 mg/dL (4.0 mmol/L).

Baseline characteristics of randomized participants

Between August 2011 and October 2013, 30,449 people (61.2% of those screened) were randomized: 15,738 from Europe, 6,082 from North America, and 8,629 from China (see Table and Supplementary Table V). Mean (SD) age was 67 (8) years and 25,534 (84%) were men. Overall, 26,679 (88%) had a history of coronary heart disease, 6,781 (22%) had a history of cerebrovascular disease, 2,435 (8%) had a history of peripheral arterial disease, and 11,320 (37%) had diabetes mellitus. The mean total cholesterol was 132 (21) mg/dL, LDL cholesterol was 61 (15) mg/dL (4,297 [14%] had LDL cholesterol ≥77 mg/dL [2.0 mmol/L]; see Supplementary Table VI), HDL cholesterol was 40 (10) mg/dL, and median (inter-quartile range) plasma triglycerides were 124 (89-174) mg/dL.

Emerging information on adherence to study treatment and event rate

At a median of 3 years of follow-up, the overall adherence to randomized study treatment was 88% and the observed blinded major coronary event rate was 2.7% per year. In November 2015, the DMC considered the guidelines for premature stopping (see Supplementary Material) and recommended that the study continue as planned. At a median follow-up of 4 years, REVEAL is anticipated to have 98% power at 2-tailed $P < .01$ to detect a 15% relative risk reduction in the primary outcome.

Discussion

The REVEAL trial seeks to assess the efficacy and safety of adding anacetrapib 100 mg daily to effective LDL-lowering treatment among 30,449 patients at high risk for cardiovascular events. The prerandomization screening and run-in phase successfully ensured that all participants were receiving appropriate doses of atorvastatin and the resulting mean baseline LDL cholesterol concentration (61 mg/dL) is in line with that anticipated in the study protocol (67 mg/dL).

Extended follow-up of a subset of DEFINE participants showed that anacetrapib has a long terminal half-life such that low levels of anacetrapib (about 8% of apparent steady-state on-treatment trough exposures and 2% of apparent steady-state peak concentrations) were detected in blood 2.5 to 4 years after cessation of therapy.[25] Preliminary data demonstrate that anacetrapib accumulates in adipose tissue and appears to have a prolonged elimination phase from fat.[26] Although drug concentrations appear to reach a plateau in plasma by 4 weeks of dosing, adipose tissue concentration of anacetrapib continues to increase for at least 16 weeks of dosing. Up to 1 year after cessation of therapy, only minimal declines in adipose levels of anacetrapib are seen despite a substantial decline in plasma concentration. Preclinical toxicology and exploratory studies performed to date have not indicated any deleterious effects of anacetrapib on adipose tissue structure or function. To explore this issue further, serial adipose tissue biopsies and plasma samples are being taken from several hundred REVEAL participants after at least 18 months of anacetrapib dosing. The planned extended follow-up of all surviving randomized participants (off treatment) will also provide valuable information on the longer-term effects of the study treatment (as has been done for a number of previous lipid treatment trials).[27-29]

By contrast with the ACCELERATE trial of evacetrapib,[18,20] the REVEAL trial of anacetrapib (which has similar effects on lipids) has recruited more participants (30,449 vs 12,092), included a lower proportion with recent acute coronary syndrome (15% vs 31%), has longer duration of follow-up (about 4 years vs around 2.5 years), and involves more primary cardiovascular events (anticipated over 3,000 vs about 1,500). Thus, the REVEAL trial will provide a robust assessment of the efficacy and safety of anacetrapib among individuals at high risk for cardiovascular events who are receiving effective LDL-lowering treatment. The main study results are anticipated later in 2017.

The REVEAL Collaborative Group

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Data Monitoring Committee: P. Sandercock (Chair), D. DeMets, J. Kjekshus, J. Neuberger, A. Tonkin; J. Emberson^{+} ($^{+}$ nonvoting DMC statistician)

Lipid Monitoring Committee: C. Granger (Chair), H. Colhoun; K. Wallendszus^{+} ($^{+}$ nonvoting statistical programmer)

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Disclosures

The Clinical Trial Service Unit at the University of Oxford (the regulatory sponsor of REVEAL) has a staff policy of not accepting honoraria or consultancy fees (see https://www.ctsu.ox.ac.uk/about/ctsu_honoraria_25june14-1.pdf).

Appendix. Supplementary material

Supplementary information, including the protocol, data analysis plan, Data Monitoring Committee Charter, and supplementary data can be found online at http://dx.doi.org/10.1016/j.ahj.2017.02.021.

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Study Type:	Interventional
Study Design:	

	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor); Primary Purpose: Treatment
Condition:	Cardiovascular Diseases
Interventions:	Drug: Evacetrapib Drug: Placebo

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
Non-Completers: Participants "Known to be Alive at Study End" is a subset of those who did not withdraw consent and later found to be alive from public sources. "Lost to follow-up" is a subset of those who did not withdraw consent for whom study end vital status could not be ascertained.

Reporting Groups

	Description
Evacetrapib	Evacetrapib 130 milligram (mg) tablet, administered orally once daily for up to 4 years. Participants will also receive standard of care for high-risk vascular disease (HRVD).
Placebo	Placebo, tablet administered orally once daily for up to 4 years. Participants will also receive standard of care for HRVD.

Participant Flow: Overall Study

	Evacetrapib	**Placebo**

STARTED	**6038**	**6054**
Received at Least One Dose of Study Drug	**6036**	**6052**
COMPLETED	**5926**	**5934**
NOT COMPLETED	**112**	**120**
Withdrawal by Subject	**49**	**51**
Known to be Alive at Study End	**54**	**62**
Lost to Follow-up	**9**	**7**

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Evacetrapib	Evacetrapib 130 mg tablet, administered orally once daily for up to 4 years. Participants received standard of care for HRVD.
Placebo	Placebo, tablet administered orally once daily for up to 4 years. Participants received standard of care for HRVD.
Total	Total of all reporting groups

Baseline Measures

	Evacetrapib	**Placebo**	**Total**
Overall Participants Analyzed [Units: Participants]	**6038**	**6054**	**12092**

Age [Units: Years] Mean (Standard Deviation)	**64.791 (9.3849)**	**64.994 (9.4591)**	**64.892 (9.4223)**
Sex: Female, Male [Units: Participants] Count of Participants			
Female	**1390**	**1394**	**2784**
Male	**4648**	**4660**	**9308**
Ethnicity (NIH/OMB) [Units: Participants] Count of Participants			
Hispanic or Latino	**500**	**522**	**1022**
Not Hispanic or Latino	**5394**	**5386**	**10780**
Unknown or Not Reported	**144**	**146**	**290**
Race (NIH/OMB) [Units: Participants] Count of Participants			
American Indian or Alaska Native	**243**	**226**	**469**
Asian	**650**	**640**	**1290**
Native Hawaiian or Other Pacific Islander	**6**	**5**	**11**
Black or African American	**141**	**153**	**294**
White	**4933**	**4971**	**9904**
More than one race	**35**	**26**	**61**
Unknown or Not Reported	**30**	**33**	**63**
Region of Enrollment [Units: Participants] Count of Participants			
Russia	**85**	**82**	**167**
Hong Kong	**24**	**28**	**52**
United States	**2235**	**2240**	**4475**

Netherlands	**171**	**169**	**340**
Austria	**34**	**34**	**68**
Sweden	**33**	**33**	**66**
China	**224**	**221**	**445**
South Korea	**87**	**94**	**181**
Poland	**243**	**240**	**483**
Brazil	**54**	**56**	**110**
Slovakia	**116**	**117**	**233**
France	**45**	**52**	**97**
Bulgaria	**113**	**118**	**231**
Lithuania	**13**	**15**	**28**
Argentina	**89**	**91**	**180**
Romania	**64**	**66**	**130**
Hungary	**118**	**115**	**233**
Japan	**205**	**202**	**407**
Ukraine	**67**	**66**	**133**
United Kingdom	**58**	**58**	**116**
Switzerland	**15**	**14**	**29**
Spain	**65**	**66**	**131**
New Zealand	**63**	**64**	**127**
Canada	**626**	**619**	**1245**
Czechia	**187**	**185**	**372**
Turkey	**1**	**2**	**3**
Belgium	**42**	**42**	**84**
Taiwan	**52**	**53**	**105**
Denmark	**95**	**100**	**195**
Italy	**43**	**40**	**83**
Mexico	**235**	**231**	**466**
South Africa	**77**	**76**	**153**
Israel	**72**	**74**	**146**
Australia	**159**	**160**	**319**
Germany	**198**	**202**	**400**

Estonia	**30**	**29**	**59**

Outcome Measures

Show All Outcome Measures

1. **Primary: Number of Participants With Composite Primary Endpoint of Cardiovascular (CV) Death, Myocardial Infarction (MI), Stroke, Coronary Revascularization, or Hospitalization for Unstable Angina (UA) [Time Frame: Baseline to Study Completion (Up to 4 years)]**

   Show Outcome Measure 1

2. **Secondary: Mean Percent Change From Baseline to 3 Months in Low-Density (LDL-C) and High-Density Lipoprotein Cholesterol (HDL-C) Levels [Time Frame: Baseline, 3 Months]**

   Show Outcome Measure 2

3. **Secondary: Number of Participants With Composite Endpoint of All-Cause Mortality, MI, Stroke, Coronary Revascularization, or Hospitalization for UA [Time Frame: Baseline through End of Study (Up to 4 years)]**

   Show Outcome Measure 3

4. **Secondary: Number of Participants With Composite Endpoint of CV Death, MI, or Coronary Revascularization [Time Frame: Baseline through End of Study (Up to 4 years)]**

   Show Outcome Measure 4

5. **Secondary: Number of Participants With Composite Endpoint of CV Death, MI, Stroke, or Hospitalization for UA [Time Frame: Baseline through End of Study (Up to 4 years)]**

   Show Outcome Measure 5

6. **Secondary: Number of Participants With Triple Composite Endpoint of CV Death, MI, or Stroke [Time Frame: Baseline through End of Study (Up to 4 years)]**

   Show Outcome Measure 6

Serious Adverse Events

Show Serious Adverse Events

Other Adverse Events

Show Other Adverse Events

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.

There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The agreement is:

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☑ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☐ Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

Results Point of Contact:

Name/Title: Chief Medical Officer
Organization: Eli Lilly and Company
phone: 800-545-5979
e-mail: ClinicalTrials.gov@lilly.com

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, Gibson CM, Granger C, Menon V, Montalescot G, Rader D, Tall AR, McErlean E, Wolski K, Ruotolo G, Vangerow B, Weerakkody G, Goodman SG, Conde D, McGuire DK, Nicolau JC, Leiva-Pons JL, Pesant Y, Li W, Kandath D, Kouz S, Tahirkheli N, Mason D, Nissen SE; ACCELERATE Investigators. Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. N Engl J Med. 2017 May 18;376(20):1933-1942. doi: 10.1056/NEJMoa1609581.

Responsible Party:	Eli Lilly and Company
ClinicalTrials.gov Identifier:	NCT01687998 History of Changes
Other Study ID Numbers:	11949
	I1V-MC-EIAN (Other Identifier: Eli Lilly and Company)
First Submitted:	September 12, 2012
First Posted:	September 19, 2012
Results First Submitted:	February 18, 2018
Results First Posted:	May 16, 2018
Last Update Posted:	May 16, 2018

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT: 800.176.089-2

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CUS: 370905835

Patente PCT
INHIBIDOR DE PROTEÍNA DE TRANSFERENCIA DEL ÉSTER DE COLESTERILO (CETP) Y COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN DICHO INHIBIDOR

Detalle del pago

Id.	Rentístico	Concepto y Servicio	Cant.	Val. Unit.	Subtotal
1	50005-01-01	Solicitud examen de patentabilidad Patente de Invención (DESCUENTO INTERNET)	1	$ 1,053,500	$ 1,053,500
		TOTAL			$ 1,053,500

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