

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.** y
mitsubishi tanabe pharma corporation

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 las sociedades **DEZIMA PHARMA B.V.** y **mitsubishi tanabe pharma corporation**, domiciliadas en Países Bajos y Japón, respectivamente, solicitantes de la patente de la referencia, en respuesta al Oficio No. **16172** notificado por comunicación electrónica el 15 de noviembre de 2017 y relacionado con concepto técnico de fondo, me permito manifestar:

1. Título

Primeramente, tomando en consideración lo expuesto por el examinador en el oficio arriba mencionado con relación al título de la presente solicitud, me permito manifestar que es deseo de los solicitantes presentar el siguiente nuevo título:

*«INHIBIDOR DE PROTEÍNA DE TRANSFERENCIA DEL ÉSTER DE
COLESTERILO (CETP) Y COMPOSICIONES FARMACÉUTICAS QUE
COMPRENDEN DICHO INHIBIDOR»*

Cabe destacar que la inclusión del nombre IUPAC del compuesto A en el título iría en contravía del propósito del mismo, el cual debe ser lo suficientemente descriptivo, pero breve. Por tanto, se manifiesta que este nuevo título es lo suficientemente claro, breve y descriptivo para referirse a la solicitud en estudio.

2. Modificaciones al capítulo reivindicatorio

Por otra parte, 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 25 reivindicaciones y reemplaza completamente al anteriormente presentado, en el cual se realizaron las siguientes modificaciones:

2.1. Las reivindicaciones 3, 4, 7 a 9, 12, 14, 15, 18 a 20 y 23 del nuevo capítulo reivindicatorio corresponden a nuevas reivindicaciones dependientes dirigidas a dosificaciones más específicas de la composición reclamada, tales como 1, 2.5 y 25 mg del Compuesto A y sus sales, las cuales encuentran soporte en el Ejemplo 2 de la presente descripción.

2.2. La reivindicación 13 del nuevo capítulo reivindicatorio corresponde a una nueva reivindicación dependiente dirigida a la composición de la presente invención que comprende la sal de hemicalcio del compuesto A.

2.3. Las reivindicaciones 4 y 5 anteriormente presentadas corresponden a las nuevas reivindicaciones 24 y 25.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud, y se realizaron con el ánimo de superar las objeciones planteadas por el examinador en su concepto técnico.

3. Pago de tasas

En relación con el número de reivindicaciones, atentamente me permito comentar que se adjunta tasa por 2 reivindicaciones adicionales, toda vez que el nuevo capítulo reivindicatorio cuenta con 2 cláusulas más que el originalmente 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.

4. **Claridad y concisión del capítulo reivindicatorio**

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, y cuentan con pleno soporte en la descripción de la solicitud en estudio, siguiendo además las recomendaciones realizadas por el examinador en su concepto técnico. En particular, frente a cada objeción, me permito señalar lo siguiente:

4.1. *«Las reivindicaciones 1-13 no son claras porque a pesar de que su encabezado se refiere a composiciones no hay describen los componentes de estas. Se recuerda al solicitante que una composición farmacéutica debe caracterizarse por sus componentes específicos tales como ingredientes activos y auxiliares de formulación, así como la proporción de estos ya que ellos son los que confieren el efecto técnico.»*

Frente a lo anterior, amablemente me permito resaltar no es necesario especificar los excipientes que pueden usarse para obtener la composición reivindicada, toda vez que una persona normalmente versada en la materia, teniendo como objetivo diseñar una composición farmacéutica adecuada, sería fácilmente capaz de seleccionarlos junto con sus cantidades. 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.

4.2. *«Las reivindicaciones 1-13 no son claras porque reclaman sales de calcio, potasio o sodio del compuesto de formula A, sin embargo, en la descripción no hay evidencia de que el solicitante hubiera obtenido dichas sales; igualmente, en los ensayos realizados no hay mención de la utilización de sales del compuesto de formula A los cuales parecen haberse desarrollado con la forma base de este compuesto.»*

En respuesta a lo anterior, me permito destacar que el documento D1 citado por el examinador en su concepto técnico, que es equivalente a su 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. Por lo tanto, me permito solicitar a ese Despacho que la objeción a este respecto sea retirada, toda vez que estas sales ya se han enseñado en la técnica y la persona normalmente versada en la materia está en capacidad de reproducirlas sin esfuerzo inventivo.

En consecuencia, me permito manifestar que el nuevo capítulo reivindicatorio adjunto al presente memorial, que incluye 25 reivindicaciones, cumple a cabalidad con las disposiciones del Artículo 30 de la Decisión 486/00.

5. Descripción

Por otro lado, en cuanto a lo señalado por el examinador sobre que: *«La descripción no divulga la invención de manera suficientemente completa para que la persona del oficio normalmente versada en la materia pueda ejecutarla toda vez que hace énfasis en los métodos de tratamiento estableciendo dosis (1, 2.5, 10 y 25 mg) y esquemas de dosificación (días 1 y 8 a 28 una vez al día) pero no se evidencia la elaboración de ninguna composición farmacéutica, lo cual es el objeto del capítulo reivindicatorio presentado.»*, me permito dirigir su atención a los datos clínicos revelados en la descripción de la solicitud en estudio, véase el Ejemplo 2, páginas 26-35, es decir, un estudio de dosis repetidas en 5 grupos de sujetos varones caucásicos de edades comprendidas entre 18 y 55 años. Cada sujeto recibió una sola dosis oral de Compuesto A/placebo el Día 1, seguida de dosis de una vez al día en los Días 8 a 35 (5 mg Compuesto A/placebo - Grupo 1) o Días 8 a 28 (1, 2.5, 10 y 25 mg de Compuesto A/placebo - Grupos 2 a 5). Todas las dosis se administraron en el centro de estudio después de un desayuno estándar. Los sujetos en cada grupo de dosis se asignaron para estudiar el tratamiento en una proporción de 10 de Compuesto A a 2 de placebo. Por lo tanto, me permito solicitar a ese Despacho que la objeción a este

respecto sea retirada, ya que es claro que la composición oral del Compuesto A está suficientemente divulgada en la memoria descriptiva de la presente solicitud.

6. Nivel inventivo

Finalmente, el examinador establece en su concepto técnico la falta de nivel inventivo de la presente solicitud en vista de las enseñanzas descritas en el documento EP1730152 (D1). No obstante, respetuosamente me permito manifestar que la novedad y el nivel inventivo de esta solicitud recaen en la sorprendente baja dosificación del compuesto A, la cual varía de 1 mg a 25 mg por día de la composición oral. Los estudios clínicos han sugerido que el Compuesto A es un potente inhibidor de la CETP. En comparación con otros inhibidores de la CETP conocidos, sólo se necesita una dosis relativamente baja de Compuesto A para alcanzar una inhibición de la CETP casi completa. Típicamente, dosis repetidas de una vez al día tan bajas como 2.5 mg de Compuesto A ya han demostrado ser suficientes para alcanzar una inhibición de la CETP casi completa (*véase* la Tabla 1 de la descripción de la presente solicitud para datos clínicos). Estas son dosis considerablemente más bajas que las que se han tenido que usar para otros inhibidores de la CETP. El primer compuesto inhibidor de la CETP en pasar a ensayos clínicos de fase 3 fue Torcetrapib, que era dosificado a 60 mg. A pesar de mostrar eficacia, Torcetrapib se retiró del desarrollo debido a problemas de seguridad, incluido un aumento inesperado de eventos cardiovasculares y muerte cuando se combinó con la atorvastatina, en comparación con la atorvastatina sola. Se demostró que un segundo inhibidor de la CETP, Dalcetrapib, era un inhibidor débil y también se ha suspendido por inutilidad en un estudio de fase 3 en el que el fármaco se dosificó a 600 mg. El tercer inhibidor de la CETP, Evacetrapib, se estaba evaluando clínicamente en una dosis diaria de 130 mg. Evacetrapib también se retiró del desarrollo debido a falta de eficacia. El cuarto inhibidor de la CETP se encuentra actualmente en ensayo de fase 3 y está siendo evaluado a una dosis de 100 mg una vez al día. Tales cantidades relativamente altas de ingredientes activos pueden conducir a varios problemas. Primero, las formas sólidas de dosificación oral, como tabletas o cápsulas, serán relativamente grandes en tamaño. Esto causa problemas al tragar tales tabletas y cápsulas. Alternativamente, se puede optar por administrar múltiples tabletas o cápsulas más pequeñas; sin embargo, esto tiene una influencia negativa en el cumplimiento y los costos del paciente. En segundo lugar, una dosis alta puede estar asociada con efectos secundarios más fuertes, que pueden tener una influencia negativa tanto en el bienestar físico del paciente como en

el cumplimiento del paciente. En tercer lugar, dado que se necesita una dosis relativamente alta para que los inhibidores de la CETP conocidos sean efectivos, tomará varios años eliminar estos inhibidores de la CETP del cuerpo (*véase* el documento Gotto *et al.* adjunto al presente memorial). En base a lo anterior, existe la necesidad de un inhibidor de la CETP potente y bien tolerado y una composición farmacéutica del mismo, que no muestre los inconvenientes mencionados anteriormente. Los estudios clínicos también han demostrado que las composiciones que contienen el Compuesto A en estas dosificaciones son bien toleradas y que no conducen a efectos secundarios graves (*véase* el Ejemplo 2 en la viñeta 3). Por ejemplo, no se observaron efectos clínicamente significativos sobre la presión sanguínea o la frecuencia cardíaca, ni el Compuesto A parece tener un efecto sobre las concentraciones séricas de electrolitos o aldosterona. Los estudios clínicos también mostraron que el Compuesto A no sufre de efectos de por alimentos y que a la dosis reivindicada no muestra efectos residuales prolongados al cesar la dosificación.

Si bien los solicitantes están de acuerdo en que el compuesto A ha sido divulgado en el documento EP1730152 (D1) citado por el examinador, el cual es equivalente a su PCT parental WO 2005/095409, dicha referencia no enseña ni sugiere la dosis baja del compuesto A que varía de 1 mg a 25 mg por día. La página 55 del documento WO 2005/095409 muestra un amplio intervalo general de dosificación de una clase de compuestos derivados de tetrahydroquinolina en la unidad de mg/kg/día, es decir, la dosis de un compuesto (I) de la presente invención o una sal farmacéuticamente aceptable del mismo varía según la ruta de administración, la edad, el peso corporal, la enfermedad y la condición/gravedad del paciente. Sin embargo, normalmente puede estar en el intervalo de aproximadamente 0.001-1.000 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. Para un paciente promedio de 60 kg, incluso la dosis preferida divulgada se traduciría en 6 mg-600 mg por día, el cual es un intervalo amplio. Los expertos en la técnica no habrían estado motivados a dosificar de 1 mg a 25 mg por día basándose en la amplia enseñanza del documento WO 2005/095409 o D1 sin experimentación adicional. Por lo tanto, la materia reivindicada es novedosa e inventiva.

En consecuencia, me permito señalar que el documento D1 no afecta 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 dicha anterioridad, demostrándose así que las reivindicaciones 1 a 25 del nuevo capítulo reivindicatorio cumplen con el requisito de nivel inventivo según los lineamientos del Artículo 18 de la Decisión 486/00.

7. Conclusión

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

7.1. 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.

7.2. La presente solicitud es patentable sobre el documento D1, 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.

8. Anexos

8.1. Nuevo capítulo reivindicatorio que comprende 25 reivindicaciones.

8.2. Artículo científico: Gotto, Jr, A. *et al.* "Evaluation of Lipids, Drug Concentration, and Safety Parameters Following Cessation of Treatment With the Cholesteryl Ester Transfer Protein Inhibitor Anacetrapibin Patients With or at High Risk for Coronary Heart Disease", *Am J Cardiol* 2014; 113:76-83.

8.3. Comprobante de pago de tasa por 2 reivindicaciones adicionales.

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

Señor Director,



CAROLINA DAZA MONTALVO

C.C. 66.783.790 de Palmira Valle

TP-141563 CSJ

notificaciones@clarkemodet.com.co

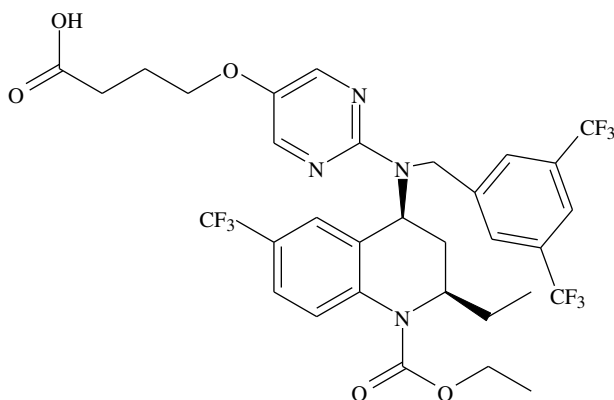
P-12186

Nuevo capítulo reivindicatorio

Febrero 12, 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.
 19. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 1 mg de sal de sodio del Compuesto A.
 20. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 2.5 mg de sal de sodio del Compuesto A.
 21. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 5 mg de sal de sodio del Compuesto A.
 22. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 10 mg de sal de sodio del Compuesto A.
 23. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la composición comprende 25 mg de sal de sodio del Compuesto A.

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.

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

Evaluation of Lipids, Drug Concentration, and Safety Parameters Following Cessation of Treatment With the Cholesteryl Ester Transfer Protein Inhibitor *Anacetrapib* in Patients With or at High Risk for Coronary Heart Disease

Antonio M. Gotto, Jr, MD, DPhil^{a,*}, Christopher P. Cannon, MD^b, Xiujiang Susie Li, PhD^c, Sanskruti Vaidya, MS, MPhil^c, Uma Kher, MS^c, Eliot A. Brinton, MD^d, Michael Davidson, MD^c, Jennifer E. Moon, PhD^a, Sukrut Shah, PhD, RPh^c, Hayes M. Dansky, MD^c, Yale Mitchel, MD^c, and Philip Barter, MD, PhD^f, for the DEFINE Investigators

The aim of this study was to assess the effects on lipids and safety during a 12-week reversal period after 18 months of treatment with anacetrapib. The cholesteryl ester transfer protein inhibitor anacetrapib was previously shown to reduce low-density lipoprotein cholesterol by 39.8% (estimated using the Friedewald equation) and increase high-density lipoprotein (HDL) cholesterol by 138.1%, with an acceptable side-effect profile, in patients with or at high risk for coronary heart disease in the Determining the Efficacy and Tolerability of CETP Inhibition With Anacetrapib (DEFINE) trial. A total of 1,398 patients entered the 12-week reversal-phase study, either after completion of the active-treatment phase or after early discontinuation of the study medication. In patients allocated to anacetrapib, placebo-adjusted mean percentage decreases from baseline were observed at 12 weeks off the study drug for Friedewald-calculated low-density lipoprotein cholesterol (18.6%), non-HDL cholesterol (17.6%), and apolipoprotein B (10.2%); placebo-adjusted mean percentage increases were observed for HDL cholesterol (73.0%) and apolipoprotein A-I (24.5%). Residual plasma anacetrapib levels (about 40% of on-treatment apparent steady-state trough levels) were also detected 12 weeks after cessation of anacetrapib. No clinically important elevations in liver enzymes, blood pressure, electrolytes, or adverse experiences were observed during the reversal phase. Preliminary data from a small cohort (n = 30) revealed the presence of low concentrations of anacetrapib in plasma 2.5 to 4 years after the last anacetrapib dose. In conclusion, after the cessation of active treatment, anacetrapib plasma lipid changes and drug levels decreased to approximately 40% of on-treatment trough levels at 12 weeks after dosing, but modest HDL cholesterol elevations and low drug concentrations were still detectable 2 to 4 years after the last dosing. © 2014 Elsevier Inc. All rights reserved. (Am J Cardiol 2014;113:76–83)

Multiple clinical trials with statins have demonstrated conclusively that reductions in low-density lipoprotein (LDL) cholesterol decrease the risk for cardiovascular events in patients with or without manifest coronary heart disease.^{1,2} In patients with existing disease, low levels of high-density lipoprotein (HDL) cholesterol is associated with increased risk even when LDL cholesterol is reduced to low levels with statin therapy.³ Inhibition of cholesteryl

ester transfer protein is a strategy under investigation for increasing HDL cholesterol levels to reduce residual cardiovascular risk. The randomized, double-blind, placebo-controlled, phase 3 trial Determining the Efficacy and Tolerability of CETP Inhibition With Anacetrapib (DEFINE) evaluated the safety of the cholesteryl ester transfer protein inhibitor anacetrapib in patients with or at high risk for coronary heart disease.⁴ In the 76-week DEFINE study, treatment with anacetrapib was associated with a placebo-adjusted 39.8% reduction in Friedewald equation-calculated LDL cholesterol (the primary efficacy end point) and a 138.1% increase in HDL cholesterol in patients treated with statins with or without other lipid-modifying agents. A subsequent assay comparison study indicated that the Friedewald equation, the method used to calculate LDL cholesterol in DEFINE, underestimates LDL cholesterol levels after treatment with anacetrapib, compared with the reference β -quantification method.⁵ Treatment with anacetrapib for 76 weeks was well tolerated, with no clinically important differences in the predefined key safety parameters, including blood pressure, electrolytes, aldosterone, and

^aOffice of the Vice President, Weill Cornell Medical College, New York, New York; ^bTIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts; ^cMerck Research Laboratories, Rahway, New Jersey; ^dUtah Foundation for Biomedical Research and Utah Lipid Center, Salt Lake City, Utah; ^eRadiant Research, Chicago, Illinois; and ^fCentre for Vascular Research, University of New South Wales, Sydney, Australia. Manuscript received May 31, 2013; revised manuscript received and accepted August 19, 2013.

This study was funded by Merck Research Laboratories, Rahway, New Jersey.

See page 82 for disclosure information.

*Corresponding author: Tel: (646) 962-6139; fax: (646) 962-1424.

E-mail address: amg2004@med.cornell.edu (A.M. Gotto).

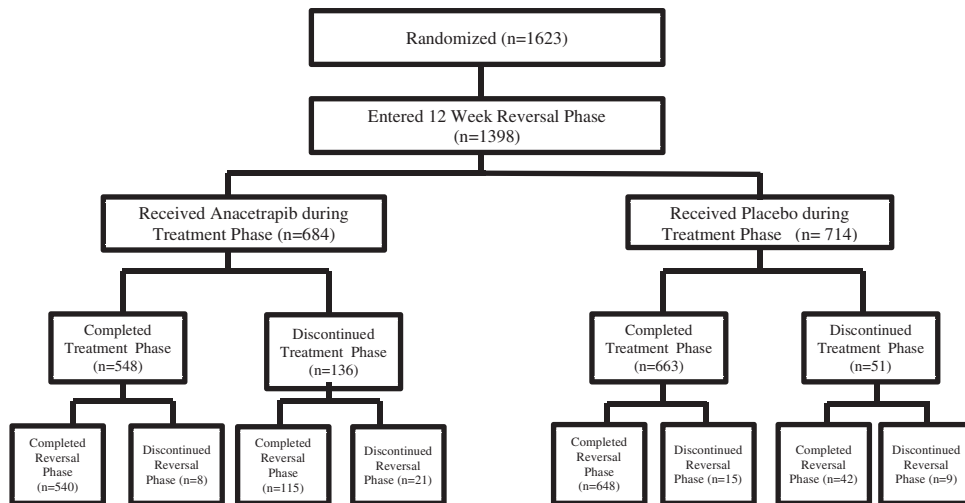


Figure 1. Disposition Consolidated Standards of Reporting Trials diagram: patients who participated in the active-treatment phase, those who entered the reversal phase, and those who completed or discontinued the reversal phase.

Table 1

Baseline (week 0) characteristics of patients in the active-treatment and reversal phases

Characteristic	Active Treatment (n = 1,623)	Reversal (n = 1,398)
Age (yrs)	62.7 ± 8.9	62.6 ± 8.8
Men	1,247 (76.8%)	1,084 (77.5%)
Hypertension*	1,101 (67.8%)	951 (68.0%)
Diabetes mellitus	862 (53.1%)	723 (53.2%)
Previous myocardial infarction†	370 (22.8%)	329 (23.5%)
Body mass index (kg/m ²)	30.2 ± 5.3	30.0 ± 5.2
Friedewald equation—calculated LDL cholesterol (mg/dl)	81.8 ± 21.0	82.4 ± 20.6
HDL cholesterol (mg/dl)	40.4 ± 9.2	40.5 ± 9.1

Data are expressed as mean ± SD or number (percentage).

* Terms included for hypertension: “blood pressure increased,” “essential hypertension,” “hypertension,” and “labile hypertension.”

† Terms included for myocardial infarction: “acute myocardial infarction” and “myocardial infarction.”

prespecified cardiovascular adjudicated events. The present report describes lipid levels, drug levels, and safety parameters after cessation of anacetrapib in the DEFINE study. Because a previous phase 2b anacetrapib dose-ranging study had observed detectable anacetrapib drug levels with residual effects on LDL cholesterol and HDL cholesterol at 8 weeks after cessation of therapy,⁶ the present study involved a 12-week off-drug follow-up period.

Methods

Details of the design, objectives, and methods of DEFINE (ClinicalTrials.gov identifier NCT00685776) have been previously reported.⁷ From April 1, 2008, to January 15, 2009, a total of 2,757 men and women aged 18 to 80 years with previous known coronary heart disease or at high risk for coronary heart disease (10-year Framingham risk score >20%) were screened from 153 centers in 20 countries. Of these, 1,697 entered the 2-week placebo run-in

phase, and 1,623 were randomized into the trial. Eligible participants had LDL cholesterol levels of 50 to 100 mg/dl (by the Friedewald equation) while taking statins with or without other lipid-modifying medications, HDL cholesterol levels <60 mg/dl, and triglyceride levels <400 mg/dl. The study protocol was reviewed and approved by the institutional review board at each participating center.

During the active-treatment phase of the trial, patients were randomized to anacetrapib 100 mg or placebo for 76 weeks (weeks 0 to 76). During the reversal phase, patients, including those who discontinued the study medication early, were followed for a 12-week period to assess the residual effects on lipids, plasma levels of anacetrapib, and safety parameters.

In addition, a substudy was initiated in the United States (PN 019-05) to determine if anacetrapib levels could be detected in the plasma of patients who were treated for up to 77 weeks and were off the study drug for ≥2 years and up to 4 years. Preliminary data are available for 48 patients previously treated with either anacetrapib (n = 30) or placebo (n = 18) from 16 sites. These patients were invited for 1 clinic visit, at which blood samples were collected to assess plasma levels of anacetrapib and to determine non-fasting LDL cholesterol (direct Genzyme assay method; Genzyme, Cambridge, Massachusetts) and HDL cholesterol (dextran-sulfate method). Anacetrapib was not detected in the plasma of any of the placebo-treated subjects. Concomitant medication data were not collected from these patients.

No specific hypotheses were prespecified in this reversal study, so all inferential analyses and results are descriptive in nature. Measurements of blood lipids and biochemical safety parameters were obtained from blood samples from patients at 12 weeks after cessation of the study medication.⁴ Lipid end points during the reversal phase were the placebo-adjusted mean percentage change from baseline (week 0) in LDL cholesterol (by the Friedewald equation), HDL cholesterol, non-HDL cholesterol, apolipoprotein B, apolipoprotein A-I, and total cholesterol after completion of the 12-week reversal period. Safety variables included adverse

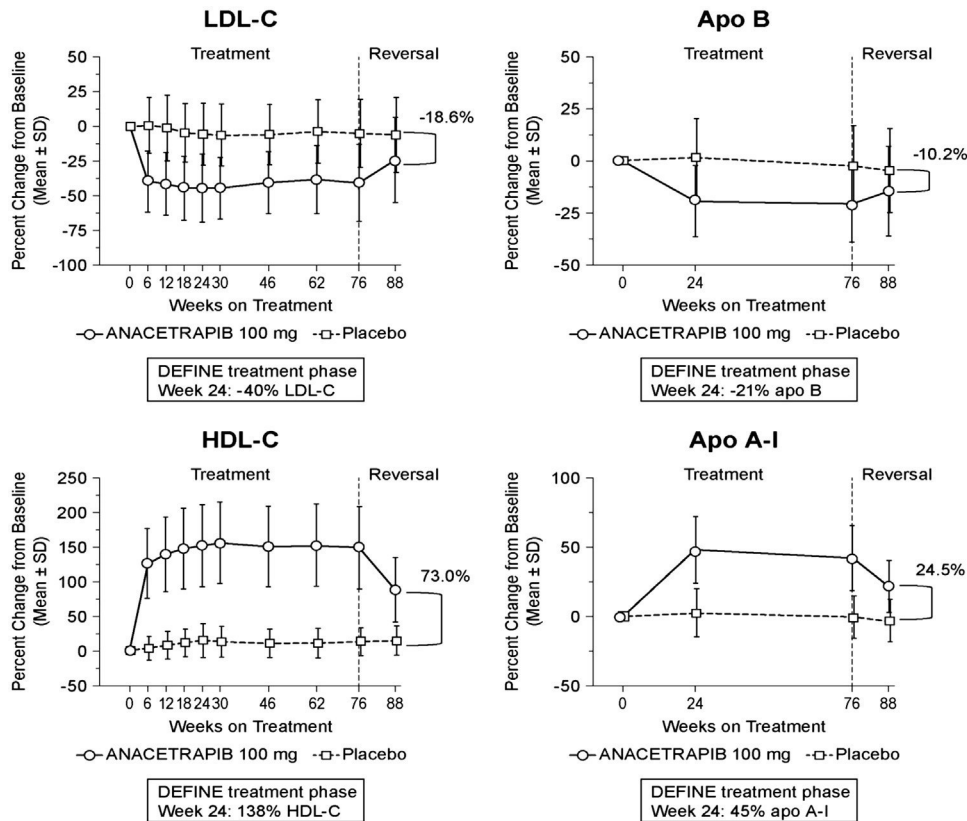


Figure 2. Changes in lipid levels during the treatment and reversal phases: mean percentage change from baseline in LDL cholesterol (LDL-C) estimated using the Friedewald equation, apolipoprotein (Apo) B, HDL cholesterol (HDL-C), and Apo A-I levels in the anacetrapib and placebo groups during the 76-week treatment period and the 12-week reversal phase. The vertical lines represent 1 SD (above and below the mean).

Table 2

Changes in low-density lipoprotein cholesterol (by the Friedewald equation) and high-density lipoprotein cholesterol in patients who completed the reversal phase after full or truncated dosing of study drug

Variable	Placebo-Adjusted Percentage Change from Baseline (95% Confidence Interval)	
	LDL Cholesterol	HDL Cholesterol
All patients in reversal [*]	-18.6 (-21.5 to -15.7)	73.0 (69.4 to 76.6)
n (anacetrapib/placebo)	641/681	655/685
Patients who completed 76 weeks of treatment [*]	-20.1 (-23.0 to -17.2)	79.3 (75.6 to 82.9)
n (anacetrapib/placebo)	519/635	530/639
Patients who discontinued during the treatment phase [†]	-11.0 (-21.5 to -0.7)	39.6 (28.1 to 52.4)
n (anacetrapib/placebo)	122/46	125/46

^{*} Difference in least squares means estimated from the analysis-of-covariance model: percentage change from baseline at week 88 = treatment + baseline.

[†] Difference in median Hodges-Lehmann estimate of the difference between treatments with a corresponding distribution-free confidence interval based on Wilcoxon's rank-sum test.

Table 3

Geometric mean (coefficient of variation) anacetrapib plasma concentrations in the active-treatment and reversal phases

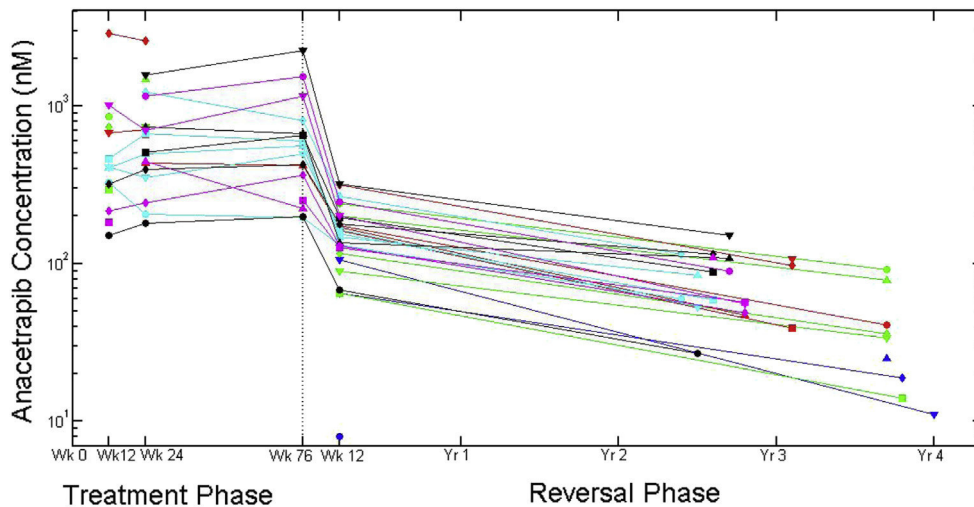
Treatment	Treatment Phase						Reversal Phase (12 Weeks After Cessation of Study Drug)	
	n	Week 12 (nmol/L)	n	Week 24 (nmol/L)	n	Week 76 (nmol/L)	n	Week 12 (nmol/L)
All available data	722	631 (73%)	575	634 (77%)	469	665 (84%)	628	201 (66%)
Trough [*] concentration	298	486 (70%)		Not available		Not available		Not applicable

^{*} Pharmacokinetic samples obtained within 19.4 to 40 hours of the last dose.

Table 4

Geometric mean (coefficient of variation) anacetrapib plasma concentrations for patients (with full or truncated study dosing) from the reversal phase with available trough data at week 12

Group	n	Treatment Phase	Reversal Phase	Reversal/Treatment Week 12 Trough Ratio
		Week 12 Trough (nmol/L)	Week 12 Concentration (nmol/L)	
Patients who completed 76 weeks of treatment	198	444 (58%)	201 (43%)	0.45
Patients who discontinued during the treatment phase	41	635 (62%)	136 (61%)	0.21



Inset:

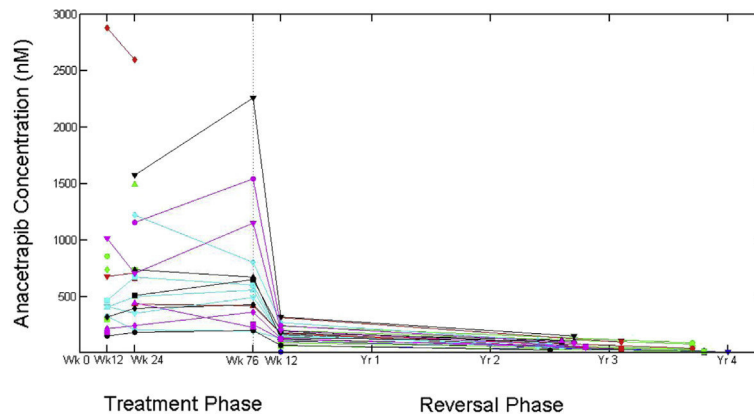


Figure 3. Changes in anacetrapib concentrations during the treatment and reversal phases: anacetrapib concentrations during the treatment phase (weeks 12, 24, and 76), at the week 12 reversal visit, and at the reversal visit 2.4 to 4 years after stopping anacetrapib. (*Inset*) The plot is shown with the y-axis in linear scale.

experiences, blood pressure, serum electrolytes, and hepatic and muscle-related enzyme levels. The prespecified cardiovascular composite end point used to evaluate cardiovascular safety included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina. All serious cardiovascular events and deaths from any cause were adjudicated by an expert committee blinded to treatment assignment and independent of the steering committee, site investigators, and study sponsor.

Blood samples were collected at visits at weeks 12, 24, and 76 during the treatment phase for determination of plasma anacetrapib concentration. The time of dosing

anacetrapib on the day before the day of the visit was recorded only for the week 12 visit. Blood samples were also collected 12 weeks after the last dose of the study medication during the reversal phase for determination of plasma anacetrapib concentrations. In patients allocated to the anacetrapib arm, the geometric means of the available plasma anacetrapib concentrations at weeks 12, 24, and 76 during the treatment phase and at the 12-week reversal phase visit were calculated. On the basis of the plasma concentration profile of anacetrapib after multiple-dose studies⁸ (unpublished data), samples collected within 19 to 40 hours of the previous dose had plasma levels within 20% of the true trough concentration. Therefore, for the 12-week

Table 5

Key safety parameters during the reversal phase: categorical variagbes

Adverse Experiences and Safety Parameters	Anacetrapib	Placebo	Absolute Difference (95% CI)	p Value
Categorical variables				
Adverse experiences				
Drug-related adverse event	2/684 (0.3%)	1/714 (0.1%)	0.2% (−0.5% to 0.9%)	0.538
Serious adverse event	21/684 (3.1%)	19/714 (2.7%)	0.4% (−1.4% to 2.3%)	0.647
Blood pressure				
Elevation in systolic blood pressure ≥10 mm Hg	188/663 (28.4%)	185/693 (26.7%)	1.7% (−3.1% to 6.4%)	0.494
Elevation in systolic blood pressure ≥15 mm Hg	114/663 (17.2%)	102/693 (14.7%)	2.5% (−1.4% to 6.4%)	0.213
Elevation in diastolic blood pressure ≥10 mm Hg	97/663 (14.6%)	74/693 (10.7%)	4.0% (0.4% to 7.5%)	0.028
Electrolytes				
Sodium greater than upper limit of normal	11/658 (1.7%)	5/686 (0.7%)	0.9% (−0.2% to 2.3%)	0.111
Chloride greater than upper limit of normal	2/658 (0.3%)	0/686 (0%)	0.3% (−0.3% to 1.1%)	0.149
Bicarbonate greater than upper limit of normal	0/660 (0%)	0/688 (0%)	0% (−0.6% to 0.6%)	>0.999
Potassium less than lower limit of normal	6/656 (0.9%)	2/683 (0.3%)	0.6% (−0.3% to 1.7%)	0.140
Liver/muscle enzymes				
Consecutive elevations of alanine aminotransferase or aspartate aminotransferase ≥3 times the upper limit of normal	1/658 (0.2%)	3/685 (0.4%)	−0.3% (−1.1% to 0.5%)	0.337
Creatine kinase ≥10 times the upper limit of normal	0/658 (0%)	0/685 (0%)	0	>0.200
Continuous variables				
	Change from baseline	Change from baseline	Least squares mean difference (95% CI)	
Blood pressure (mm Hg)				
Systolic	1.4	1.1	0.3 (−1.1 to 1.7)	0.668
Diastolic	0.3	0.1	0.2 (−0.6 to 1.0)	0.617
Electrolytes (mEq/L)				
Sodium	−1.1	−1.5	0.3 (0.1 to 0.5)	0.006
Chloride	−1.5	−1.8	0.2 (−0.1 to 0.5)	0.136
Bicarbonate	−0.1	−0.2	0.1 (−0.1 to 0.4)	0.359
Potassium	0	0	0 (−0.1 to 0)	0.339
Liver enzymes (IU/L)				
Aspartate aminotransferase	−0.5	0.1	−0.6 (−1.4 to 0.2)	0.121
Alanine aminotransferase	−1.4	−1.2	−0.2 (−1.4 to 1.0)	0.715

CI = confidence interval.

Table 6

Cardiovascular events during the 12-week reversal phase

Event	Anacetrapib (n = 684)	Placebo (n = 714)
Prespecified adjudicated cardiovascular events	1 (0.1%)	4 (0.6%)
Cardiovascular death	0 (0%)	1 (0.1%)
Nonfatal myocardial infarction	0 (0%)	1 (0.1%)
Unstable angina pectoris	0 (0%)	2 (0.3%)
Nonfatal stroke	1 (0.1%)	0 (0%)
Death from any cause	1 (0.1%)	1 (0.1%)
Revascularization	2 (0.3%)	1 (0.1%)

active-treatment phase visit, samples collected within 19 and 40 hours of the previous dose were defined as trough samples.

The primary efficacy analysis was based on a 12-week interval (i.e., end of study drug dosing to end of the 12-week reversal period). An analysis-of-covariance model was used for percentage change from baseline (week 0) at the 12-week reversal visit for LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and total cholesterol; the analysis-of-covariance model included a term for treatment and used the respective lipid baseline term as a covariate. The treatment difference in terms of percentage change from baseline at

the week 12 reversal visit was estimated from this model. Between-group estimates and 95% confidence intervals were provided for the anacetrapib versus placebo treatment groups. A sensitivity analysis was also performed to examine the effects on LDL cholesterol and HDL cholesterol and anacetrapib plasma levels for patients who discontinued early in the study and for patients who completed the 76 weeks of treatment. Key safety variables or adverse events of special interest were summarized for all patients who entered the reversal phase up to and including the 12-week reversal visit.

Results

Of the 1,623 patients randomized in the 76-week active-treatment phase of the DEFINE study, a total of 1,398 entered the reversal-phase study after cessation of the study drug. Two types of patients entered the 12-week reversal phase: (1) those who previously completed the 76-week treatment phase and (2) those who discontinued early (Figure 1). Baseline patient characteristics were similar between the active treatment and reversal phases (Table 1).

Evidence of a drug effect on lipid end points was observed after completion of the 12-week reversal period in patients allocated to the anacetrapib arm. At 12 weeks after

cessation of anacetrapib, placebo-adjusted mean percentage reductions from baseline (week 0) were observed for LDL cholesterol (18.6%) estimated by the Friedewald equation, apolipoprotein B (10.2%), and non-HDL cholesterol (17.6%) (Figure 2). Mean percentage increases in HDL cholesterol (73.0%) and apolipoprotein A-I (24.5%) were also evident (Figure 2). These placebo-adjusted treatment effects on lipids after the reversal period were approximately 50% to 60% of those observed during the active-treatment phase. In patients who discontinued treatment early ($n = 136$), who had a median duration of treatment of 170 days, the effects on LDL cholesterol and HDL cholesterol 12 weeks after stopping therapy were smaller than in the patients who completed the 76-week treatment phase of therapy (Table 2).

Anacetrapib plasma concentrations were relatively constant at weeks 12, 24, and 76 of the treatment phase (Table 3). The geometric mean trough concentration at week 12 was 486 nmol/L in the subset of 298 patients from the treatment phase with available trough measurements. At 12 weeks after cessation of anacetrapib, the geometric mean anacetrapib concentration for all patients from the reversal phase was approximately 60% lower than the on-treatment geometric mean trough level. In the subset of 239 patients from the reversal phase with available trough concentrations at week 12 of the treatment phase, those who completed the 76-week treatment had a geometric mean anacetrapib concentration at the end of the reversal period that was 55% lower than the geometric mean trough concentration at the 12-week on-treatment time point; for those who discontinued treatment early, this level was 79% lower (Table 4).

Anacetrapib levels were also assessed in 30 patients who were previously treated with anacetrapib for time periods ranging from 1 to 77 weeks but who did not enter the 2-year extension study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00685776) identifier NCT00685776). These patients were off the study drug for 2.4 to 4 years. Residual anacetrapib levels were still present at levels that are expected to indicate low pharmacologic activity (Figure 3). The median percentage change in HDL cholesterol was an 18.1% residual increase from baseline in patients who were off treatment with anacetrapib for up to 4 years, compared with a 122.5% increase at the end of the treatment phase. However, this estimate needs to be interpreted cautiously because concomitant therapy information is not currently available for these patients.

During the 12-week reversal phase of the study, there were no patterns of clinically important differences in liver enzymes, blood pressure, electrolytes, or adverse experiences between the anacetrapib group and the placebo group (Table 5). In 4 of the 5 measures of blood pressure, there were no significant differences between the 2 groups; however, there was a significant difference in the percentage of patients with increases in diastolic blood pressure of ≥ 10 mm Hg (Table 5). A total of 97 patients (14.6%) in the anacetrapib group experienced elevations in diastolic blood pressure of ≥ 10 mm Hg during the reversal phase, compared with 74 (10.7%) in the placebo group ($p = 0.028$). Still, there were no significant differences between treatment groups in the mean change from baseline (week 0) for systolic or diastolic blood pressure or in the percentage

of subjects with increases of ≥ 10 or ≥ 15 mm Hg in systolic blood pressure (Table 5, Supplementary Figure 1). There were also no significant between-group differences in serum levels of chloride, bicarbonate, or potassium (Table 5). With regard to serum levels of sodium, there was no significant difference between treatment groups in the percentage of patients with values greater than the upper limit of the normal range at the 12-week reversal visit. However, the mean changes in sodium levels from baseline to the 12-week reversal visit were -1.1 and -1.5 mmol/L in the anacetrapib and placebo groups, respectively ($p = 0.006$).

During the 12-week reversal phase, the prespecified, adjudicated composite cardiovascular end point used to evaluate safety occurred in 1 patient in the anacetrapib group (0.1%) and 4 (0.6%) in the placebo group (Table 6).

Discussion

Anacetrapib is a potent cholesteryl ester transfer protein inhibitor with robust, dose-dependent effects on LDL cholesterol and HDL cholesterol levels.^{9,10} During the 76-week active-treatment phase of the DEFINE study, anacetrapib 100 mg increased HDL cholesterol levels by 138.1%, decreased LDL cholesterol levels by 39.8% as calculated by the Friedewald formula, and decreased non-HDL cholesterol levels by 31.7% compared with placebo.⁴ At the end of the 12-week reversal phase, there were residual effects on lipids (approximately 50% to 60% of on-treatment effects) roughly proportional to the presence of residual anacetrapib plasma levels (about 40% of the apparent steady-state on-treatment trough levels). Residual low drug levels (about 7% to 8% of apparent steady-state on-treatment trough concentration levels, projected to be about 1% to 2% of on-treatment peak levels) could also still be detected in the plasma up to 4 years after cessation of anacetrapib.

These data indicate that the terminal half-life of anacetrapib is longer than previously estimated from phase 1⁸ and phase 2^{6,11} studies of shorter duration. During an 8-week reversal period after an 8-week, phase 2b dose-ranging study, residual drug concentrations (18% to 26% of on-treatment concentrations) and treatment effects on LDL cholesterol and HDL cholesterol were observed in groups receiving the higher doses of anacetrapib as monotherapy and in combination with atorvastatin.⁶ This finding, coupled with the results of this investigation, are consistent with a multiphase elimination period. Interestingly, patients who discontinued early in the present study had smaller residual effects on lipids and lower anacetrapib drug concentrations after the 12-week reversal phase compared with patients who completed the study (Table 2). These data suggest that treatment duration may have an impact on the washout kinetics of anacetrapib. Further evidence for multiphase elimination was observed in the preliminary data from the 30 patients with residual anacetrapib plasma concentrations detected 2.5 to 4 years after cessation of dosing. Although off-drug plasma sampling was performed at only 2 time points, the initial decrease in plasma anacetrapib concentrations at 12 weeks was much more rapid than the slow decrease observed between 12 weeks and 2.5 to 4 years.

The washout of anacetrapib from plasma appears to be slower than its accumulation in that compartment. Plasma

samples collected during the treatment phase in the DEFINE trial indicate comparable plasma levels at weeks 12, 24, and 76, with the caveat that the actual interval between dosing and sampling was obtained only for the week 12 visits. Additional studies with more frequent plasma sampling will further refine the estimates of the terminal half-life of anacetrapib.

The mechanism for the delayed plasma clearance of anacetrapib is currently under investigation. Anacetrapib is a lipophilic compound. Preclinical and clinical studies indicate that anacetrapib enters adipose tissue, and this phenomenon appears to contribute to the delayed clearance from the body (unpublished data). Additional preclinical and clinical studies are currently under way to further characterize and probe the mechanism(s) of the terminal half-life of anacetrapib.

As was true during the treatment phase, during the reversal phase, there were no clinically meaningful differences in liver enzymes, blood pressure, electrolytes, or adverse experiences between treatment groups. Although 1 measure of blood pressure showed a categorical increase in diastolic blood pressure (≥ 10 mm Hg) in the anacetrapib versus placebo group during the reversal period, no increase was observed for systolic blood pressure. Furthermore, no changes were observed between groups for the potentially more sensitive measures of continuous change from baseline for systolic and diastolic blood pressure. Additionally, the active-treatment phase of the trial revealed no alterations in blood pressure with anacetrapib treatment.⁴ Because the categorical elevation in diastolic blood pressure is not reflected in any other blood pressure measure obtained during either the active-treatment or reversal phases of the DEFINE trial, this isolated finding may represent a type 1 error, or “false-positive” finding.

In previous clinical studies, anacetrapib has been well tolerated, with no significant differences in adverse experiences between the anacetrapib and placebo treatment groups. At this point, it is difficult to determine the clinical significance of the delayed clearance of anacetrapib. The results of ongoing studies will provide additional data on the long terminal half-life and potential impact on adverse events. The results of the active treatment phase of the DEFINE study, which indicated that anacetrapib did not produce off-target adverse effects such as increases in cardiovascular morbidity and mortality as were observed with torcetrapib, provided the impetus for the initiation of a definitive cardiovascular outcomes study with anacetrapib. The ongoing Randomized Evaluation of the Effects of Anacetrapib Through Lipid-Modification (REVEAL) will randomize 30,000 patients with occlusive arterial disease to treatment with anacetrapib 100 mg or placebo against a background of atorvastatin therapy (*ClinicalTrials.gov* identifier NCT01252953). That study will provide a comprehensive evaluation of the efficacy and safety of cholesteryl ester transfer protein inhibition with anacetrapib.

Acknowledgment: We thank Manash Shankar Chatterjee and Sherry Liu (at Merck) for their support for the statistical analysis and comments during the preparation of this report.

Disclosures

Dr. Gotto serve on the board of directors of Aegerion Pharmaceuticals and Arisaph Pharmaceuticals; as a consultant for AstraZeneca, Janssen, Kowa, Merck, and Roche; and on advisory boards for Dupont and Vatera Capital. Dr. Cannon receives research grants/support from Accumetrics, AstraZeneca, CSL-Behring, Essentialis, GlaxoSmithKline, Merck, Regeneron, Sanofi, and Takeda; serves on advisory boards for Alnylam, Bristol-Myers Squibb, Lipimedix, and Pfizer but donates funds to charity; and is a clinical advisor and has equity in Automedics Medical Systems. Dr. Brinton serves on a medical advisory board for Atherotech, Inc.; receives compensation for consultancy and lectures from Abbott Laboratories, AstraZeneca, Merck & Co., Bristol-Myers Squibb, Daiichi Sankyo Inc., Kaneka Pharma America, Takeda Pharmaceuticals, Kowa Pharmaceuticals, GlaxoSmithKline, Boehringer Ingelheim, LipoScience Inc., Amarin Pharmaceuticals, Health Diagnostics Laboratory, Roche/Genentech, Essentialis, Arisaph; and receives research grants from Abbott Laboratories, Merck & Co., Amarin Pharmaceuticals, Health Diagnostics Laboratory, and Roche/Genentech. Dr. Davidson serves on speakers' bureaus for Abbott and Merck; is on advisory boards or consults for Abbott, Aegerion, Amgen, AstraZeneca, Daiichi-Sankyo, Esperion, iMD (Intelligent Medical Decisions), Kinemed, LipoScience, Merck, Novo Nordisk, Omthera, Professional Evaluation, Inc., Roche, sanofi-aventis, Synarc, Takeda, and Vindico; receives grant or research support from Abbott, Merck, sanofi-aventis, and Amgen; and has equity or serves on the board of directors for Omthera (Chief Medical Officer), Professional Evaluation, Inc. Medical Education Company (Board of Directors), and Sonogene (Board of Directors). Dr. Barter serves on advisory boards for MSD and Kowa; serves as a consultant for CSL-Behring; receives grant support from MSD, Pfizer, and Roche; and receives payments for lectures from MSD, AstraZeneca, Pfizer and Kowa. Drs. Li, Shah, Dansky, and Mitchel, Sanskruti Vaidya, and Uma Kher are employees of and have stock/stock options in Merck & Co, Inc. Dr. Moon has no disclosures.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.amjcard.2013.08.041>.

1. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670–1681.
2. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, Ward K, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2011;1: CD004816.
3. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC; Treating to New Targets Investigators. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 2007;357:1301–1310.
4. Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AM, Stepanavage M, Liu SX, Gibbons P, Ashraf TB, Zafarino J, Mitchel Y, Barter P; Determining the Efficacy and Tolerability

- Investigators. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* 2010;363:2406–2415.
5. Davidson M, Liu SX, Barter P, Brinton EA, Cannon CP, Gotto AM Jr, Leary ET, Shah S, Stepanavage M, Mitchel Y, Dansky HM. Measurement of LDL-C after treatment with the CETP inhibitor anacetrapib. *J Lipid Res* 2013;54:467–472.
 6. Dansky HM, Bloomfield D, Gibbons P, Liu S, Sisk CM, Tribble D, McKenney JM, Littlejohn TW III, Mitchel Y. Efficacy and safety after cessation of treatment with the cholesteryl ester transfer protein inhibitor anacetrapib (MK-0859) in patients with primary hypercholesterolemia or mixed hyperlipidemia. *Am Heart J* 2011;162:708–716.
 7. Cannon CP, Dansky HM, Davidson M, Gotto AM Jr, Brinton EA, Gould AL, Stepanavage M, Liu SX, Shah S, Rubino J, Gibbons P, Hermanowski-Vosatka A, Binkowitz B, Mitchel Y, Barter P; DEFINE Investigators. Design of the DEFINE trial: Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib. *Am Heart J* 2009;158:513–519.
 8. Krishna R, Bergman AJ, Jin B, Fallon M, Cote J, Van Hoydonck P, Laethem T, Gendrano IN III, Van Dyck K, Hilliard D, Laterza O, Snyder K, Chavez-Eng C, Lutz R, Chen J, Bloomfield DM, De Smet M, Van Bortel LM, Gutierrez M, Al-Huniti N, Dykstra K, Gottesdiener KM, Wagner JA. Multiple-dose pharmacodynamics and pharmacokinetics of anacetrapib, a potent cholesteryl ester transfer protein (CETP) inhibitor, in healthy subjects. *Clin Pharmacol Ther* 2008;84:679–683.
 9. Krishna R, Anderson MS, Bergman AJ, Jin B, Fallon M, Cote J, Rosko K, Chavez-Eng C, Lutz R, Bloomfield DM, Gutierrez M, Doherty J, Bieberdorf F, Chodakewitz J, Gottesdiener KM, Wagner JA. Effect of the cholesteryl ester transfer protein inhibitor, anacetrapib, on lipoproteins in patients with dyslipidaemia and on 24-h ambulatory blood pressure in healthy individuals: two double-blind, randomized placebo-controlled phase I studies. *Lancet* 2007;370:1907–1914.
 10. Bloomfield D, Carlson GL, Sapre A, Tribble D, McKenney JM, Littlejohn TW III, Sisk CM, Mitchel Y, Pasternak RC. Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients. *Am Heart J* 2009;157:352–360.
 11. Teramoto T, Shirakawa M, Kikuchi M, Nakagomi M, Tamura S, Surks HK, Sisk CM, Numaguchi H. Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib in Japanese patients with dyslipidemia. *Atherosclerosis* 2013;230:52–60.



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT: 800.176.089-2

COMPROBANTE DE RECAUDO SISTEMA SIPI

Radicado: NC2016/0000629

Recibo: 18-9808

Fecha: 12/02/2018

CAROLINA MERCEDES DAZA MONTALVO

CC: 66.783.790

Pago PSE No: 152840

CUS: 314101710

Patente PCT

INHIBIDOR DE PROTEÍNA DE TRANSFERENCIA DEL ÉSTER DE COLESTERILO (CETP) Y COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN EL INHIBIDOR PARA USO EN EL TRATAMIENTO O PREVENCIÓN DE ENFERMEDADES CARDIOVASCULARES

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

Sede Centro: Carrera 13 No.27-00 Pisos 3,4,5 y 10 Bogotá D.C. - Colombia

Web: www.sic.gov.co e-mail: contactenos@sic.gov.co Conmutador: (571)5870000 Contact Center: (571)5920400