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29 October 2015

(54) Title: METHODS FOR REDUCING REMNANT CHOLESTEROL AND OTHER LIPOPROTEIN FRACTIONS BY ADMINISTERING AN INHIBITOR OF PROPROTEIN CONVERTASE SUBTILISIN KEXIN-9 (PCSK9)

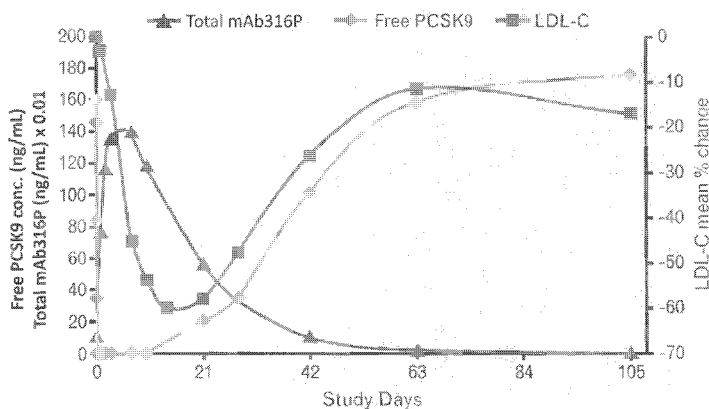


Figure 1

(57) Abstract: The present invention provides methods for reducing various lipoprotein fractions in the serum of patients. The methods of the invention include reducing serum remnant cholesterol, and/or the serum concentration of one or more LDL-C subfractions in a patient. The methods of the present invention comprise selecting a patient who exhibits elevated serum lipoproteins, and administering to the patient a pharmaceutical composition comprising a PCSK9 inhibitor. In certain embodiments, the PCSK9 inhibitor is an anti-PCSK9 antibody such as the exemplary antibody referred to herein as mAb316P.

WO 2014/194168 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/040163

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/00 A61K39/395 A61P9/10 C07K16/40
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/154999 A1 (AMGEN INC [US]; CHAN JOYCE CHI YEE [US]; GIBBS JOHN P [US]; DIAS CLAPT) 15 November 2012 (2012-11-15) figures 24,25; examples 22,23 -----	1,2, 20-39
X	WO 2013/039969 A1 (REGENERON PHARMA [US]; SWERGOLD GARY [US]) 21 March 2013 (2013-03-21) examples 1-5; sequences 90,92 ----- -/--	1,2, 20-39

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 8 September 2015	Date of mailing of the international search report 16/09/2015
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Cilensek, Zoran
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/040163

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANETTE VARBO ET AL: "Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease", JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 61, no. 4, 1 January 2013 (2013-01-01), pages 427-436, XP055136401, ISSN: 0735-1097, DOI: 10.1016/j.jacc.2012.08.1026 page 427; figures 1-4 -----	1,2, 20-39
A	A. B. JORGENSEN ET AL: "Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction", EUROPEAN HEART JOURNAL, vol. 34, no. 24, 17 December 2012 (2012-12-17), pages 1826-1833, XP055136634, ISSN: 0195-668X, DOI: 10.1093/eurheartj/ehs431 page 1827, left-hand column; figures 1-4 -----	1,2, 20-39
A	KAWASHIRI MASA-AKI ET AL: "Statin Therapy Improves Fractional Catabolic Rate of LDL without Affecting Impaired VLDL and VLDL Remnant Catabolism in Homozygous FH Patient Due to PCSK9 Gene Mutation: Evidence from Kinetic Study with Stable Isotope", CIRCULATION, vol. 126, no. 21, Suppl. S, November 2012 (2012-11), page 13869, XP009179823, & AMERICAN-HEART-ASSOCIATION RESUSCITATION SCIENCE SYMPOSIUM; LOS ANGELES, CA, USA; NOVEMBER 03 -04, 2012 the whole document -----	1,2, 20-39
X,P	TOTH PP ET AL: "Alirocumab, a Proprotein Convertase Subtilisin/Kexin Type 9 Monoclonal Antibody, Reduces Cholesterol Concentrations of Serum Remnant Lipoprotein Fractions, Very Low-Density Lipoproteins and Triglycerides):", CIRCULATION, vol. 128, no. 22, Suppl., 17 November 2013 (2013-11-17), page 17492, XP055136391, ISSN: 0009-7322 the whole document -----	1,2, 20-39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/040163

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 2(completely); 20-39(partially)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2(completely); 20-39(partially)

A method for reducing serum remnant cholesterol in a patient, the method comprising selecting a patient with elevated serum remnant cholesterol, and administering to the patient a pharmaceutical composition comprising a PCSK9 inhibitor.

2. claims: 3, 4(completely); 20-39(partially)

A method for reducing serum VLDL in a patient, the method comprising selecting a patient with elevated serum VLDL, and administering to the patient a pharmaceutical composition comprising a PCSK9 inhibitor.

3. claims: 5, 6(completely); 20-39(partially)

A method for reducing serum VLDL1+2-C in a patient, the method comprising selecting a patient with elevated serum VLDL, 12-C, and administering to the patient a pharmaceutical composition comprising a PCSK9 inhibitor.

4. claims: 7, 8(completely); 20-39(partially)

A method for reducing serum VLDL3-C in a patient, the method comprising selecting a patient with elevated serum VLDL 3-C, and administering to the patient a pharmaceutical composition comprising a PCSK9 inhibitor.

5. claims: 9, 10(completely); 20-39(partially)

A method for reducing serum IDL-C in a patient, the method comprising selecting a patient with elevated serum IDL-C, and administering to the patient a pharmaceutical composition comprising a PCSK9 inhibitor.

6. claims: 11-19(completely); 20-39(partially)

A method for reducing the serum concentration of at least one low-density lipoprotein cholesterol (LDL-C) subfraction in a patient, the method comprising selecting a patient with an elevated serum level of at least one LDL-C subfraction, and administering to the patient a pharmaceutical composition comprising a PCSK9 inhibitor.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/040163

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012154999	A1	15-11-2012	
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		TW 201329099 A	16-07-2013
		US 2013243784 A1	19-09-2013
		WO 2013039969 A1	21-03-2013
