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A61K 39/395 (2006.01)  C07K 16/40 (2006.01)

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(34) Designated States (unless otherwise indicated, for every kind of regional protection available): ARipo (BW, GH, [Continued on nextpage])

(54) Title: METHODS FOR TREATING PATIENTS WITH HYPERCHOLESTEROLEMIA THAT IS NOT ADEQUATELY CONTROLLED BY MODERATE-DOSE STATIN THERAPY

Figure 1

Clinical Trial Design:
Patients inadequately Controlled by Moderate-Dose Atorvastatin (ATV) Therapy (20mg or 40mg daily)

Double-blind treatment period (24 weeks)

N=169

Entry status:
atorvastatin 20 mg

N=88

Entry status:
atorvastatin 40 mg

N=27

Entry status:
atorvastatin placebo

Alirocumab 75 mg + ATV 20 mg + E2L-placebo (n=57)

Patients with CVD and LDL-C>20 mg/dl or CVD risk factors and LDL-C>100 mg/dl.

Alirocumab-placebo + ATV 30 mg + E2L 10 mg (n=55)

Alirocumab-placebo + ATV 40 mg + E2L-placebo (n=57)

Alirocumab 75 mg + ATV 40 mg + E2L-placebo (n=47)

Alirocumab-placebo + ATV 40 mg + E2L 10 mg (n=47)

Alirocumab-placebo + ATV 80 mg + E2L-placebo (n=45)

Alirocumab-placebo + ATV 80 mg + E2L 10 mg (n=45)

(57) Abstract: The present invention provides methods for treating hypercholesterolemia. The methods of the present invention comprise administering to a 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. The methods of the present invention are useful for treating patients with hypercholesterolemia that is not adequately controlled by moderate-dose statin therapy.
WO 2015/123423 A3


Published:

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

— with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:

8 October 2015

with international search report (Art. 21(3))
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K39/00 A61K39/395 A61P9/10 C07K16/40

According to International Patent Classification (IPC) unto 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, BIOSIS, EMBASE, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>WO 2013/039969 A1 (REGENERON PHARMA [US]; SWERGOLD GARY [US]) 21 March 2013 (2013-03-21) examples 3-5; sequences 90, 92</td>
<td>1-12, 21-25</td>
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</table>

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

"Z" document member of the same patent family

Date of the actual completion of the international search

21 May 2015

Date of mailing of the international search report

19/08/2015

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

Ciensek, Zoran

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page 1 of 3
**INTERNATIONAL SEARCH REPORT**

**DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<td>X</td>
<td>JAMES M. MCKENNEY ET AL: &quot;Safety and Efficacy of a Monoclonal Anti-body to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease, SAR236553/REGN727, in Patients with Primary Hypercholesterolemia and Receiving Ongoing Stable Atorvastatin Therapy&quot;, JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 59, no. 25, 1 June 2012 (2012-06-01), pages 2344-2353, XP055049859, ISSN: 0735-1097, DOI: 10.1016/j.jacc.2012.03.007 page 2352, left-hand column, lines 7-11; table 1-3</td>
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<td>X, P</td>
<td>JENNI FER G. ROBINSON ET AL: &quot;Efficacy and Safety of Alirocumab as Add-on Therapy in High-Cardiovascular Disease-Related Patients with Hypercholesterolemia Not Adequately Controlled with Atorvastatin (20 or 40 mg) or Rosuvastatin (10 or 20 mg): Design and Results of the ODYSSEY OPTIONS Studies&quot;, CLINICAL CARDIOLOGY, vol. 37, no. 10, 30 September 2014 (2014-09-30), pages 597-604, XP055187779, ISSN: 0160-9289, DOI: 10.1002/clc.22327 figure 1; tables 1-3</td>
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<td>X,P</td>
<td>HELEN M COLHOUN ET AL: &quot;Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximal tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials&quot;, BMC CARDIOVASCULAR DISORDERS, BIOMED CENTRAL, LONDON, GB, vol. 14, no. 1, 20 September 2014 (2014-09-20), page 121, ISSN: 1471-2261, DOI: 10.1186/1471-2261-14-121, figure 1; tables 1-2</td>
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The whole document
# INTERNATIONAL SEARCH REPORT

**Information on patent family members**

**International application No**

PCT/US2015/015633

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<td>a. Forming part of the international application as filed:</td>
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<td>b. [□] Furnished together with the international application under PCT Rule 13fer1 (a) for the purposes of international search only in the form of an Annex C/ST.25 text file.</td>
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<td>2.</td>
<td>In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.</td>
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Form PCT/ISA/21 0 (continuation of first sheet (1)) (January 2015)
INTERNATIONAL SEARCH REPORT

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.:

   I-12 (completely) ; 21-25 (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.
1. claims: 1-12 (completely) ; 21-25 (partially)

A method for treating a patient with hypercholesterolemia, the method comprising administering one or more doses of a PCSK9 inhibitor to the patient, wherein the patient exhibits hypercholesterolemia that is not adequately controlled by a moderate-dose statin therapy in the absence of the PCSK9 inhibitor.

2. claims: 13-20 (completely) ; 21-25 (partially)

A therapeutic method comprising: (a) selecting a patient who is on a moderate-dose statin therapy and who exhibits a serum low-density lipoprotein cholesterol (LDL-C) level of greater than about 70 mg/dL after at least four weeks of receiving the moderate-dose statin therapy; and (b) administering to the patient one or more initial doses of a pharmaceutically acceptable composition comprising 75 mg of an anti body or anti-gen-bi nding fragment thereof that specifically binds hPCSK9 ("the 75 mg doses") in combination with the moderate-dose statin therapy; and (c) if the patient has not achieved a serum LDL-C level of less than 70 mg/dL following administration of one or more of the 75 mg doses, then: (i) discontinuing administration of the 75 mg doses; and (ii) administering to the patient one or more additional doses of a pharmaceutically acceptable composition comprising 150 mg of the anti body or anti-gen-bi nding fragment thereof that specifically binds hPCSK9 ("the 150 mg doses") wherein each dose of anti body or anti-gen-bi nding fragment thereof is administered to the patient once every two weeks.

3. claim: 26

A therapeutic method comprising: (a) selecting a patient who is on a moderate-dose statin therapy and who exhibits a serum low-density lipoprotein cholesterol (LDL-C) level of greater than about 70 mg/dL after at least four weeks of receiving the moderate-dose statin therapy; (b) administering to the patient one or more initial doses of a pharmaceutically acceptable composition comprising 75 mg of an anti body or anti-gen-bi nding fragment thereof that specifically binds hPCSK9 ("the 75 mg doses") in combination with the moderate-dose statin therapy; and (c) if the patient has not achieved a serum LDL-C level of less than 70 mg/dL following administration of one or more of the 75 mg doses, then: (i) discontinuing administration of the 75 mg doses; and (ii) administering to the patient one or more additional doses of a pharmaceutically acceptable composition comprising 150 mg of the anti body or anti-gen-bi nding fragment thereof that specifically binds hPCSK9 ("the 150 mg doses") wherein each dose of anti body or anti-gen-bi nding fragment thereof is administered to the patient once every two weeks.

4. claims: 27 (completely) ; 31-35 (partially)

A method for treating a patient with hypercholesterolemia, the method comprising administering multiple doses of an anti-PCSK9 antibody to the patient at a dosage amount of about 75 to 150 mg per dose, and a dosing frequency of about once every two weeks, wherein the patient exhibits...
hypercholesterolemia that is not adequately controlled by a moderate-dose statin therapy in the absence of the anti-PCSK9 antibody, wherein the moderate-dose statin therapy comprises a daily dose of about 20 mg of atorvastatin, and wherein, after about 24 weeks of treatment with the anti-PCSK9 antibody in combination with the moderate-dose statin therapy, the patient exhibits a reduction in LDL-C level from baseline of about 44%.

5. Claims: 28 (completely); 31-35 (partly)

A method for treating a patient with hypercholesterolemia, the method comprising administering multiple doses of an anti-PCSK9 antibody to the patient at a dosing amount of about 75 to 150 mg per dose, and a dosing frequency of about once every two weeks, wherein the patient exhibits hypercholesterolemia that is not adequately controlled by a moderate-dose statin therapy in the absence of the anti-PCSK9 antibody, wherein the moderate-dose statin therapy comprises a daily dose of about 40 mg of atorvastatin, and wherein, after about 24 weeks of treatment with the anti-PCSK9 antibody in combination with the moderate-dose statin therapy, the patient exhibits a reduction in LDL-C level from baseline of about 54%.

6. Claims: 29 (completely); 31-35 (partly)

A method for treating a patient with hypercholesterolemia, the method comprising administering multiple doses of an anti-PCSK9 antibody to the patient at a dosing amount of about 75 to 150 mg per dose, and a dosing frequency of about once every two weeks, wherein the patient exhibits hypercholesterolemia that is not adequately controlled by a moderate-dose statin therapy in the absence of the anti-PCSK9 antibody, wherein the moderate-dose statin therapy comprises a daily dose of about 10 mg of rosuvastatin, and wherein, after about 24 weeks of treatment with the anti-PCSK9 antibody in combination with the moderate-dose statin therapy, the patient exhibits a reduction in LDL-C level from baseline of about 51%.

7. Claims: 30 (completely); 31-35 (partly)

A method for treating a patient with hypercholesterolemia, the method comprising administering multiple doses of an anti-PCSK9 antibody to the patient at a dosing amount of about 75 to 150 mg per dose, and a dosing frequency of about once every two weeks, wherein the patient exhibits hypercholesterolemia that is not adequately controlled by a moderate-dose statin therapy in the absence of the anti-PCSK9 antibody, wherein the moderate-dose statin therapy comprises a daily dose of about 20 mg of
rosuvastatin n, and wherein, after about 24 weeks of treatment with the anti-PCSK9 antibody in combination with the moderate-dose statin therapy, the patient exhibits a reduction in LDL-C level from baseline of about 36%.

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