

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IB2015/055986

International filing date (day/month/year)
06.08.2015

Priority date (day/month/year)
07.08.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/22 A61K39/395 A61P3/00

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Saame, Tina

Telephone No. +49 89 2399-0



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
 - ☒ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ 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.
5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 3, 7-27(completely); 4-6, 28-33(partially)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☒ no international search report has been established for the whole application or for said claims Nos. 3, 7-27(completely); 4-6, 28-33(partially)
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).
- ☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1, 2(completely); 4-6, 28-33(partially)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>4-6, 31-33(all partially)</u>
	No: Claims	<u>1, 2(completely); 28-30(partially)</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1, 2(completely); 4-6, 28-33(partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>1, 2(completely); 4-6, 28-33(partially)</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV

Lack of unity of invention

- 1 This Authority considers that the application does not meet the requirements of unity of invention and that there are 9 inventions covered by the claims indicated as follows:
1. claims: 1, 2(completely); 4-6, 28-33(partially)
antibodies against angiopoietin-like 4 (ANGPTL4) or fragments thereof which inhibit the binding of LPL to ANGPTL4;
compositions comprising such antibodies and therapeutic uses of such antibodies
 2. claims: 3(completely); 4-6, 28-33(partially)
antibodies against ANGPTL4 or fragments thereof which bind to human ANGPTL4 with a KD of 45 pM or less (measured by ForteBio kinetic binding assay) or 24 pM or less (measured by SET assay); compositions comprising such antibodies and therapeutic uses of such antibodies
 3. claims: 14, 21(completely); 7-13, 28-33(partially)
antibodies against ANGPTL4 which comprise a heavy chain CDR3, heavy and/or light chain variable regions or all six CDRs of the exemplified antibodies NEG276 and NEG276-LALA;
compositions comprising such antibodies and therapeutic uses of such antibodies
 4. claims: 15, 22(completely); 7-13, 28-33(partially)
antibodies against ANGPTL4 which comprise a heavy chain CDR3, heavy and/or light chain variable regions or all six CDRs of the exemplified antibody NEG278; compositions comprising such antibodies and therapeutic uses of such antibodies
 5. claims: 16, 23(completely); 7-13, 28-33(partially)
antibodies against ANGPTL4 which comprise a heavy chain CDR3, heavy and/or light chain variable regions or all six CDRs of the exemplified antibody NEG310; compositions comprising such antibodies and therapeutic uses of such antibodies
 6. claims: 17, 24(completely); 7-13, 28-33(partially)

antibodies against ANGPTL4 which comprise a heavy chain CDR3, heavy and/or light chain variable regions or all six CDRs of the exemplified antibody NEG313; compositions comprising such antibodies and therapeutic uses of such antibodies

7. claims: 18, 25(completely); 7-13, 28-33(partially)

antibodies against ANGPTL4 which comprise a heavy chain CDR3, heavy and/or light chain variable regions or all six CDRs of the exemplified antibody NEG315; compositions comprising such antibodies and therapeutic uses of such antibodies

8. claims: 19, 26(completely); 7-13, 28-33(partially)

antibodies against ANGPTL4 which comprise a heavy chain CDR3, heavy and/or light chain variable regions or all six CDRs of the exemplified antibody NEG318; compositions comprising such antibodies and therapeutic uses of such antibodies

9. claims: 20, 27(completely); 7-13, 28-33(partially)

antibodies against ANGPTL4 which comprise a heavy chain CDR3, heavy and/or light chain variable regions or all six CDRs of the exemplified antibody NEG319; compositions comprising such antibodies and therapeutic uses of such antibodies

- 2 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

Article 3(4)(iii) in combination with Rule 13.1 PCT stipulates that the international application shall relate to one invention only or to a group so linked as to form a single general inventive concept. Rule 13.2 PCT stipulates that where a group of inventions is claimed in one and the same international application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding 'special technical features', i.e. technical features that define a novel and inventive contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Group 1 of inventions solves the technical problem of providing ANGPTL4 antibodies which inhibit LPL binding to ANGPTL4.

Group 2 of inventions solves the technical problem of providing ANGPTL4 antibodies which bind to ANGPTL4 with a picomolar affinity.

Groups 3-9 of inventions solve the technical problem of providing ANGPTL4 antibodies.

The only common concept (technical relationship) linking the above groups of inventions is that they relate to ANGPTL4 antibodies.

However, this concept cannot be regarded as the 'single general inventive concept' required by Rule 13.1 PCT because it is neither novel nor inventive. Lee et al (D1; see below) had disclosed the monoclonal antibody 14D12 which is specific for ANGPTL4 (see e.g. abstract).

Since no other 'special technical feature' (Rule 13.2 PCT) could be identified to provide a linking concept between the different groups there is lack of unity and each group must be regarded as a separate group of inventions.

The applicant is furthermore requested to note that in principle, group 1 as set out above can be further subdivided since the monoclonal antibody 14D12 disclosed by Lee et al. (D1; see below) was furthermore disclosed to inhibit the binding of LDL to ANGPTL4 (see e.g. figure 2). This objection may become relevant upon entry into the regional phase of the present international application.

- 3 In response to the invitation to restrict or pay additional fees, the applicant has not paid additional fees. The following examination report thus only relates to the invention first mentioned in the claims (i.e. group 1).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Subject-matter of the application

The present application relates to a set of (humanized) monoclonal antibodies against human ANGPTL4. The antibodies are shown to block human ANGPTL4 inhibition of lipoprotein lipase (table 4) and are thus useful in the treatment of lipid metabolic disorders.

2 Documents

Reference is made to the following documents:

- D1 E-C. LEE ET AL: "Identification of a New Functional Domain in Angiopoietin-like 3 (ANGPTL3) and Angiopoietin-like 4 (ANGPTL4) Involved in Binding and Inhibition of Lipoprotein Lipase (LPL)", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 284, no. 20, 15 May 2009 (2009-05-15), pages 13735-13745, XP055035574, ISSN: 0021-9258, DOI: 10.1074/jbc.M807899200
- D2 WO 2006/074228 A1 (LEXICON GENETICS INC [US]; LEE E-CHIANG [US]; LANDES GREGORY M [US]; C) 13 July 2006 (2006-07-13)
- D3 WO 2011/079257 A2 (REGENERON PHARMA [US]; SLEEMAN W MARK [US]; GUSAROVA VIKTORIA [US]; KI) 30 June 2011 (2011-06-30)

3 Novelty (Article 33(2) PCT)

- 3.1 Document D1 disclosed the monoclonal antibody 14D12 which is specific for ANGPTL4 (see e.g. abstract). mAb 1D12 is shown to inhibit the binding of ANGPTL4 to LPL (see figure 2). Thus, the subject-matter of claims 1 and 2 lacks novelty over D1.
- 3.2 Similar objections can be based on document D2 which is a patent application originating from several of the authors of D1. D2 disclosed monoclonal antibodies that specifically bind to ANGPTL4 and neutralize at least one activity of ANGPTL4 (claim 1), wherein the monoclonal antibody is a humanized monoclonal antibody (claim 3), wherein the monoclonal antibody increases LPL activity (claim 5) and wherein the monoclonal antibody is 14D12 (claim 9). The 14D12 antibody of D2 seems to be the same antibody as disclosed in D1 (see above). mAb 14D12 is shown to rescue LPL activity (paragraph 272 and figure 15), by virtue of its blocking the binding between LPL and ANGPTL4.

Thus, the subject-matter of claims 1 and 2 lacks novelty over D2.

D2 furthermore disclosed pharmaceutical compositions comprising such antibodies (claim 54) and methods of treating a disorder of lipid metabolism such as hypertriglyceridemia, hypercholesterolemia, obesity or diabetes with such antibodies (claims 55, 57-60). Hence, the subject-matter of claims 28-30 lacks novelty over D2.

- 3.3 Similar objections can be based on document D3. D3 disclosed ANGPTL4 antibodies which are shown to inhibit ANGPTL4's inhibitory activity against LPL (example 5). It must *a priori* be assumed that this effect is mediated by disrupting the association between ANGPTL4 and LPL. Thus, claims 1 and 2 lack novelty over D3.

D3 furthermore disclosed a pharmaceutical composition comprising such antibodies (claim 19) and methods for preventing or treating a disease or disorder which is prevented, ameliorated, improved or inhibited by reduction or inhibition of ANGPTL4 activity, comprising administering to a subject in need thereof a therapeutically effective amount of an ANGPTL4 antibody wherein the disease or disorder is selected from hypertriglyceridemia, hypercholesterolemia, chylomicronemia, atherogenic dyslipidemia, a cardiovascular disease or disorder, acute pancreatitis, nonalcoholic steatohepatitis (NASH), diabetes and obesity (claims 22 and 23). Thus, also the subject-matter of claims 28-30 lacks novelty over D3.

4 Inventive step (Article 33(3) PCT)

- 4.1 Dependent claims 31-33 do not disclose additional features which are on their own sufficient to establish an inventive step of the claimed subject-matter over any of D1-D3.
- 4.2 Dependent claims 4-6 further define the claimed antibodies by one or more CDRs comprised within the antibody sequences. The subject-matter of these claims solves the technical problem of providing *further/alternative* ANGPTL4 antibodies which can inhibit the binding of ANGPTL4 to LPL, thus counteracting the inhibitory activity of ANGPTL4 on LPL. In the absence of a technical effect which sets these *alternatives* apart from the antibodies described in the above cited prior art, no inventive step can be acknowledged. Their provision must be regarded as the result of routine laboratory practice.
- 4.3 It is also noted that IF there were a technical effect which could account for the acknowledgement of inventive step, then the claimed antibodies would have to be defined by the structural features which are responsible for achieving this particular technical effect. In the context of antibodies, these structural features are generally the sequences of both variable domains. The present

claims only contain partial information concerning the antibody sequences, i.e. they relate to single CDRs (claim 4), a plethora of possible combinations of CDRs (claim 5), CDRs with sequences variations (claim 6) etc.

5 Method of treatment

Claims 29-31 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment. Patentability, in particular novelty and inventive step, of claims 29-31 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Re Item VIII

Certain observations on the international application

- 1 Claims 4-6 contravene the requirements of Article 6 PCT since the claims shall not rely, in respect of the technical features of the invention, on references to the description (including tables) or drawings (Rule 6.2(a) PCT).
- 2 Present claim 1 relates to an ANGPTL4 antibody *or fragment thereof*. In the absence of a functional limitation of such fragments, the claim has *in principle* to be interpreted in its broadest possible meaning, i.e. relating to any arbitrarily short fragment of an ANGPTL4 antibody. Under such interpretations, further novelty objections would have to be raised in view of e.g. isolated Fc fragments etc.