

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|                                                    |                                                                                                  |                                                                                     |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Applicant's or agent's file reference<br>23876     | <b>FOR FURTHER ACTION</b><br>see Form PCT/ISA/220<br>as well as, where applicable, item 5 below. |                                                                                     |
| International application No.<br>PCT/US2015/061445 | International filing date ( <i>day/month/year</i> )<br>19 November 2015 (19-11-2015)             | (Earliest) Priority Date ( <i>day/month/year</i> )<br>21 November 2014 (21-11-2014) |
| Applicant<br><br>MERCK SHARP & DOHME CORP.         |                                                                                                  |                                                                                     |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 9 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out 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))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box No. II)

3. ☒ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant  
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant  
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1  
☒ as suggested by the applicant  
☐ as selected by this Authority, because the applicant failed to suggest a figure  
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

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### Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out 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 13~~ter~~.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 13~~ter~~.1(a)).
    - ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
2. ☐ 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.
3. Additional comments:

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## 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.: 1-73, 75-81(all partially)  
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:  
see FURTHER INFORMATION sheet PCT/ISA/210
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.:  
1-4, 6-13, 16-33, 36-43, 46-51, 54-60, 63-81(all 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.

## INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER  
 INV. C07K14/62 A61K38/28 A61K47/48  
 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)

C07K A61K

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 2014/052451 A2 (UNIV INDIANA RES & TECH CORP [US]) 3 April 2014 (2014-04-03)<br>cited in the application<br><br>claim 1; figures 22F, 22G<br>-----                 | 1-4,<br>6-13,<br>16-33,<br>36-43,<br>46-51,<br>54-60,<br>63-81 |
| X         | WO 00/50456 A2 (AVENTIS PHARMA GMBH [DE];<br>HOECKER HARTWIG [DE]; HAVENITH CHANTALLE<br>[DE] 31 August 2000 (2000-08-31)<br><br>abstract; claims 1,2<br>-----<br>-/- | 1-4,<br>6-13,<br>16-33,<br>36-43,<br>46-51,<br>54-60,<br>63-81 |



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

16 March 2016

Date of mailing of the international search report

17/06/2016

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

Griesinger, Irina

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International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                        | Relevant to claim No.                                                       |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| X         | <p>DEPPE ET AL: "Structure-activity relationship of covalently dimerized insulin derivatives: correlation of partial agonist efficacy with cross-linkage at lysine B29", NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, SPRINGER, DE, vol. 350, no. 2, 1 August 1994 (1994-08-01), pages 213-217, XP000925874, ISSN: 0028-1298 figure 1</p> <p>-----</p> | <p>1-4,<br/>6-13,<br/>16-33,<br/>36-43,<br/>46-51,<br/>54-60,<br/>63-81</p> |
| X         | <p>SCHUETTLER ET AL: "Preparation and Properties of Covalently Linked Insulin Dimers", HOPPE-SEYLER'S ZEITSCHRIFT FUER PHYSIOLOGISCHE CHEMIE, WALTER DE GRUYTER, BERLIN, DE, vol. 363, no. 3, 1 March 1982 (1982-03-01), pages 317-330, XP000925886, ISSN: 0018-4888 abstract</p> <p>-----</p>                                                            | <p>1-4,<br/>6-13,<br/>16-33,<br/>36-43,<br/>46-51,<br/>54-60,<br/>63-81</p> |
| A         | <p>JOHN P MAYER ET AL: "Insulin Structure and Function", BIOPOLYMERS, JOHN WILEY &amp; SONS, INC, US, vol. 88, no. 5, 1 January 2007 (2007-01-01), pages 687-713, XP008152505, ISSN: 0006-3525, DOI: 10.1002/BIP.20734 [retrieved on 2007-04-04] abstract</p> <p>-----</p>                                                                                | <p>1-4,<br/>6-13,<br/>16-33,<br/>36-43,<br/>46-51,<br/>54-60,<br/>63-81</p> |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/061445

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| WO 2014052451                             | A2                  | 03-04-2014                 |                     |
|                                           |                     | AU 2013323669 A1           | 26-03-2015          |
|                                           |                     | CA 2886228 A1              | 03-04-2014          |
|                                           |                     | CN 104981251 A             | 14-10-2015          |
|                                           |                     | EP 2900255 A2              | 05-08-2015          |
|                                           |                     | JP 2015532283 A            | 09-11-2015          |
|                                           |                     | US 2015274802 A1           | 01-10-2015          |
|                                           |                     | WO 2014052451 A2           | 03-04-2014          |
| -----                                     |                     |                            |                     |
| WO 0050456                                | A2                  | 31-08-2000                 |                     |
|                                           |                     | AT 428729 T                | 15-05-2009          |
|                                           |                     | AU 765076 B2               | 11-09-2003          |
|                                           |                     | AU 3160100 A               | 14-09-2000          |
|                                           |                     | CA 2363639 A1              | 31-08-2000          |
|                                           |                     | CN 1341122 A               | 20-03-2002          |
|                                           |                     | CY 1109241 T1              | 02-07-2014          |
|                                           |                     | DE 19908041 A1             | 31-08-2000          |
|                                           |                     | DK 1161452 T3              | 17-08-2009          |
|                                           |                     | EP 1161452 A2              | 12-12-2001          |
|                                           |                     | ES 2324093 T3              | 30-07-2009          |
|                                           |                     | HK 1042710 A1              | 13-01-2006          |
|                                           |                     | JP 4519324 B2              | 04-08-2010          |
|                                           |                     | JP 2003525864 A            | 02-09-2003          |
|                                           |                     | PT 1161452 E               | 08-07-2009          |
|                                           |                     | US 2002160938 A1           | 31-10-2002          |
|                                           |                     | WO 0050456 A2              | 31-08-2000          |
|                                           |                     | ZA 200106971 A             | 29-01-2003          |
| -----                                     |                     |                            |                     |

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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

1. claims: 1-4, 6-13, 16-33, 36-43, 46-51, 54-60, 63-81(all partially)

relate to "Dimer 1" as shown in claim 74, said compound comprising two insulins, wherein each insulin respectively comprises an A and a B chain linked by two disulfide bridges and wherein the A chain comprises a further disulfide bridge and wherein the two insulins are linked by the linker shown for "Dimer 1" in claim 74 and variants of "Dimer 1" having the same linker and a similar structure; the corresponding compositions and medical uses.

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2. claims: 1-81(partially)

relate to "Dimer 2" as shown in claim 74, said compound comprising two insulins, wherein each insulin respectively comprises an A and a B chain linked by two disulfide bridges and wherein the A chain comprises a further disulfide bridge and wherein the two insulins are linked by the linker shown for "Dimer 2" in claim 74 and variants of "Dimer 2" having the same linker and a similar structure; the corresponding compositions and medical uses.

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- 3-94. claims: 1-93(partially)

relate to "Dimer 3" to "Dimer 94" as shown in claim 74, said compounds comprising two insulins, wherein each insulin respectively comprises an A and a B chain linked by two disulfide bridges and wherein the A chain comprises a further disulfide bridge and wherein the two insulins are linked by the linker shown for "Dimer 3" to "Dimer 94" in claim 74, respectively and variants of dimers 3-94 having respectively the same linker and a similar structure; the corresponding compositions and medical uses.

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**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box II.2

Claims Nos.: 1-73, 75-81(all partially)

The subject-matter of claims 1-73 and 75-81 is not supported by the description and not sufficiently disclosed (Articles 5 and 6 PCT), since it is only defined by the desired property without providing the corresponding structural features. According to the claims, the compounds are supposed to be an "insulin receptor partial agonist" or "insulin analog dimer". However, according to the application, the specific combination of features, namely (1) the sequence of the insulin or insulin analog, (2) the type and length of the linker, (3) the position of the amino acids linked by the linker and (4), optionally, the substituent at the N-terminus of the A or B chain, is responsible for the property of the dimer. The application does not seem to comprise any general teaching how said features need to be combined in order to achieve a desired property. Hence, the skilled practitioner needs to rely on trial and error in order to identify an insulin receptor partial agonist or insulin analog dimer. Consequently, the subject-matter of the afore-mentioned claims does not fulfill the requirements of Articles 5 and 6 PCT.

Independent of the lack of clarity due to the lack of structural features, it is not clear from the claims what the applicant considers to be the contribution to the art for the following reasons. Claims 1, 11, 21, 31, 41, 49, 57, 74, 82 and 88 are formulated as independent claims, wherein claims 1, 11, 21, 31 and 57 relate to an insulin receptor partial agonist, claims 41, 49 and 88 to an insulin analog dimer, claim 82 to an insulin dimer and claim 74 to a compound without providing any function. Hence, the present set of claims comprises numerous independent claims of the same category, wherein the products are not interrelated. Therefore, the present set of claims lacks conciseness making it as a whole unclear. The lack of clarity is even more pronounced due to the fact that the whole set of claims comprises 63 pages and that claim 74 lists on 44 pages 94 compounds, wherein each compound could be considered to be an independent claim. Furthermore, claims 82-93 relate to an insulin dimer comprising a linker defined by an arbitrary number, which seems to refer to the linkers 1-50 provided in the table on pages 49-59 of the description. However, not all linkers of the dimers listed in claim 74 are also listed in the table of the linkers. For example, the linker of "Dimer 1" does not seem to be disclosed in the table of the linkers. Furthermore, the application does not provide any indication which linker is used in which dimer, i.e. an indication for the correspondence between dimers listed in claim 74 and linkers listed in the table in the description. In conclusion, the way the claims are drafted makes it impossible to identify what the applicant considers to be the contribution to the art.

Furthermore, the contribution to the art is not clear from the description. It is disclosed in the description of the application that insulin and insulin analogs are well-known in the art (see e.g. description: page 21, lines 6 to page 23, line 5). Furthermore, insulin dimers are well-known in the art (description: page 27, lines 7-18). In addition, the presence of a substituent at the N-terminus of at least one A or B chain cannot be the

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

invention, since said feature is not present in all claims (see e.g. claim 21, where the substituent is optional). Furthermore, prior art documents such as D1 seem to disclosed all common features of the dimers of the application (see in particular Figures 22F and G). According to the description, the inventors have discovered that the level of insulin activity and partial agonist activity of the dimers is a function of the dimeric structure, the sequence of the insulin analog, the length of the dimerization linker and the site of dimerization that connects the two insulin polypeptides (description: page 27, lines 18-23). Hence, it seems that the applicant sees the contribution to the art in the specific combination of the features (1) the sequence of the insulin or insulin analog, (2) the type and length of the linker, (3) the position of the amino acids linked by the linker and (4), optionally, the substituent at the N-terminus of the A or B chain. The only claim which clearly defines the combination of the four features is claim 74, which lists the structure of 94 dimers.

In conclusion, the deficiencies under Articles 5 and 6 PCT are to such an extent that the subject-matter of the claims can not be searched completely. Therefore, the search has to be limited to the structurally defined compounds of dimers 1-94 of claim 74 and variants having the same linker and a similar structure and dimers as defined in claims 82-93.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.