

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43*bis*.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/US2015/061445

International filing date (day/month/year)
19.11.2015

Priority date (day/month/year)
21.11.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/62 A61K38/28 A61K47/48

Applicant
MERCK SHARP & DOHME CORP.

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 43*bis*.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 66.1*bis*(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:



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Date of completion of
this opinion

see form
PCT/ISA/210

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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. 5, 14, 15, 34, 35, 44, 45, 52, 53, 61, 62, 82-93(completely); 1-4, 6-13, 16-33, 36-43, 46-51, 54-60, 63-81(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. 1-73, 75-81(all partially) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ the claims, or said claims Nos. 1-73, 75-81(all partially) are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ no international search report has been established for the whole application or for said claims Nos. 5, 14, 15, 34, 35, 44, 45, 52, 53, 61, 62, 82-93(completely); 1-4, 6-13, 16-33, 36-43, 46-51, 54-60, 63-81(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 13~~ter~~.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. 1-4, 6-13, 16-33, 36-43, 46-51, 54-60, 63-81(all 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>1-4, 6-13, 16-33, 36-43, 46-51, 54-60, 63-81(all partially)</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-4, 6-13, 16-33, 36-43, 46-51, 54-60, 63-81(all partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>1-4, 6-13, 16-33, 36-43, 46-51, 54-60, 63-81(all 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

1 Application and cited documents

The present application relates to an insulin dimer comprising a linker which does not include a disulfide bond. It is shown 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. Said dimers are said to have the advantage of having a reduced risk of promoting hypoglycemia (description page 27, lines 18-23).

The following documents are cited in the international search report.

- D1 WO 2014/052451 A2 (UNIV INDIANA RES & TECH CORP [US])
3 April 2014, cited in the application
- D2 WO 00/50456 A2 (AVENTIS PHARMA GMBH [DE]; HOECKER
HARTWIG [DE]; HAVENITH CHANTALLE [DE]) 31 August 2000
- D3 DEPPE ET AL: NAUNYN-SCHMIEDEBERG'S ARCHIVES OF
PHARMACOLOGY, SPRINGER, DE, vol. 350, no. 2, 1 August
1994, pages 213-217, XP000925874
- D4 SCHUETTLER ET AL: 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
- D5 JOHN P MAYER ET AL: BIOPOLYMERS, JOHN WILEY &
SONS, INC, US,
vol. 88, no. 5, 1 January 2007, pages 687-713, XP008152505

D1 discloses an insulin dimer which acts as a partial agonist having less than 66% of the activity of native insulin, said dimer comprising a first and a second insulin, respectively comprising an A and a B chain linked by disulfide bridges and wherein the carboxy-terminus of the B chains are linked e.g. by polyethyleneglycol (Figures 22F and G).

D2 discloses covalently bridged insulin dimers, wherein the insulins comprise the A and B chains linked by two disulfide bonds and the two B chains being linked preferably by a dicarbonic acid (Abstract and claims 1 and 2).

D3 discloses insulin dimers, wherein the insulin B chains of the dimer are linked by the lysine at position 29 using a dicarboxylic acid of two, eight or twelve carbons. The effect of the structure on the activity of the dimer is analysed.

D4 discloses symmetrical and asymmetrical insulin dimers, their preparation and properties (Figures 1 and 6). In particular, the potency and biological activities of the dimers (lipogenesis and binding) are analyzed (Tables 2 and 3).

D5 is a review on the structure and function of insulin analogues and on the effect of specific amino acid modifications.

2 **Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- 2.1 Before issuing the present international search report and the corresponding search opinion, the applicant was informed that the application was considered not to fulfill the requirements of clarity, sufficiency and unity to such an extent that a complete search was impossible. The reasons for said deficiencies were explained and the applicant was asked to clarify the subject-matter to be searched. The applicant did not reply to said informal **request for clarification**. Therefore, the present international search report and the corresponding search opinion do not cover all subject-matter claimed, but are restricted to the subject-matter which is clear, supported and enabling as far as it relates to invention 1, namely essentially to "Dimer 1" shown in claim 74 and variants thereof having the same linker and a similar structure and to uses thereof. The reasons are as follows.
- 2.2 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.

- 2.3 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**.

- 2.4 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 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.

- 2.5 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**(see also lack of unity objection).

3 **Re Item IV**

Lack of unity of invention

- 3.1 The application as filed is considered to lack unity of invention since its subject-matter relates not to one but rather to at least 94 separate inventions not linked together by a common underlying inventive concept as required by Rule 13.1 PCT.

The claims and the inventions to which the at least 94 separate inventions relate may be grouped as indicated in the international search report.

According to Rule 13.2 PCT, an international patent application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features. Special technical features are such features that define the contribution of the claimed invention over the prior art.

- 3.2 The identified 94 inventions involve the **technical feature** of "insulin receptor agonists consisting of dimers of insulin or insulin analogs linked by a linker, wherein each insulin or insulin analog is composed of an A and a B chain linked by disulfide bonds and wherein the linker bridges the lysines at position 29 of the B chain and has a carbonyl group at each end". However, this feature cannot be accepted to constitute a special technical feature because it

does not define a contribution to the prior art. For example, the documents D3 and D4 already disclose dimerized insulin derivatives which are cross-linked at lysine B29 by a dicarboxylic acid (see D3: title and Figure 1 and D4: Figure 1).

- 3.3 Some of the inventions have furthermore in common that their amino-terminus is modified, in particular as an amid. Said modification at the amino terminus is called "**substituent**" in the claims (see e.g. paragraph 3 of claim 1). However, said modification is well-known in the art. For example, D1 discloses in figure 22F insulin dimers comprising an amid group at the N-terminus and a linker between lysines of the B chain, wherein the linker comprises two carbonyl groups. Hence, the modification of the amino-terminus cannot be the common technical feature of some of the claims.
- 3.4 Finally, the identified inventions do not have a common inventive concept based on their **function**. According to the application, 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. It is continued that at least some of the dimers of the application have a reduced risk of promoting hypoglycemia when administered in high doses than native insulin or other insulin analogs when administered at high doses (description: page 27, lines 18-23). However, it is well-known in the art that the activity of an insulin dimer depends on the above-listed features. For example, D4 provides a study of the effect of the position and structure of the linker (see D4: Abstract and Tables 2 and 3). Furthermore, the reduced risk of hypoglycemia for insulin dimers which act as a partial agonist is already disclosed in D1 (see e.g. D1: page 6, lines 29-31 and page 7, lines 21-23). Consequently, neither the vaguely indicated structure-function relationship nor the reduced risk of hypoglycemia for some of the dimers can be the common inventive concept of the present application.
- 3.5 The objective **problem** underlying the present application is the provision of further insulin dimers which act as insulin agonists or partial agonists. The solution for invention 1 consists in the provision of "Dimer 1" of claim 74 and variants thereof having the same linker and general structure. The solution for invention 2 consists in the provision of "Dimer 2" of claim 74 and variants thereof having the same linker and general structure. The solution for inventions 3-94 consists respectively in the provision of Dimers 3-94 of claim

74 and of variants thereof having the same linker and general structure. These solutions are not so linked as to form one single inventive concept (Rule 13.1 PCT).

Searching these different subjects would have caused major additional searching efforts.

- 3.6 **Remark:** Claims 82-93 are defined by reference to a linker disclosed in a table on pages 49-59 of the description. If the structure of the linker is the same as in one of the dimers listed in claim 74, the subject-matter of claims 82-93 is grouped with the invention characterized by the specific dimer. If the structure of the linker is not the same as in one of the dimers listed in claim 74, then it gives rise to a further invention. In this case the present application may comprise more than the indicated 94 inventions. Therefore, if the applicant requests a further search, he should clearly indicate the subject-matter to be searched, i.e. the common structural features characterizing the invention to be searched and also the basis in the application for said subject-matter.

4 **Re Item V**

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

Invention 1: "Dimer 1" of claim 74

- 4.1 Claims 68, 69, 76 and 77 are directed to a method of treatment of the human or animal body. No unified criteria exist in the PCT contracting states regarding said claims. However, when entering the regional phase before the European patent office, an objection has to be expected, since methods of treatment are exempt from patentability.
- 4.2 The subject-matter of the present application as far as it relates to invention 1 is **novel**. None of the cited prior art documents discloses an insulin dimer with the same linker.
- 4.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of all claims as far as relating to invention 1 does **not involve an inventive step** in the sense of Article 33(3) PCT.

The "Dimer 1" of claim 74 consists of the natural sequences of the A and B chain of human insulin (SEQ ID NOs: 1 and 2) with a disulfide bridge within the A chain between the cysteine residues 6 and 11 and a disulfide bridge between the A and B chains at cysteines A7/B7 and A20/B19. The bridge

between the two insulins is formed between the lysine B29 and consists of 2,2'-(ethane-1,2-diylbis(oxy))diacetyl) (see example 15, page 126f.).

According to Table 15 (description: page 161) the dimers showed in a ligand competition assay an IC_{50} of 1.50nM and in a functional Akt-phosphorylation assay 50.5% of the activity of Humulin. Hence, "Dimer 1" seems to be a partial agonist of the insulin receptor.

D3 may be considered as closest prior art document. D3 discloses dimerized human insulin, having the same sequence and the same disulfide bridges as the insulin in the dimer of the application and a linker between the B chains using the lysines B29. The **difference** to the claimed subject-matter consists in the structure of the linker - a dicarboxylic acid in D3 and the modified dicarboxylic acid 2,2'-(ethane-1,2-diylbis(oxy))diacetyl) in invention 1 of the present application. This difference does not seem to have any effect, since the dimers of the prior art and the dimer of invention 1 of the application all act as partial agonists (see e.g. D3: Abstract). Hence, the objective **problem** is formulated as the provision of a further insulin dimer cross-linked at lysine B29 by a dicarboxylic acid having partial agonistic activity. The solution, namely the linker of "Dimer 1" is not inventive. In particular, the skilled practitioner was motivated to try a linker with ether bridges, since such bridges are already present in other linkers of insulin dimers. For example, D1 discloses linking of insulin using polyethylene glycol (PEG). Furthermore, he had a reasonable expectation of success to obtain a partial agonist, since the insulin dimers of D3 comprising the dicarboxylic acid linker and the dimers of D1 comprising the PEG linker act as partial agonists. Hence, the subject-matter of invention 1 is obvious in view of D3 alone or in combination with D1.

5 **Re Item VIII**

Certain observations on the international application

The objections under Articles 5 and 6 PCT were already discussed under item III of the present communication, since they resulted in a restriction of the searched subject-matter.