

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

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/US2015/036328

International filing date (day/month/year)
18.06.2015

Priority date (day/month/year)
23.06.2014

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/48 A61P3/00 C07K14/475

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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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>2-14, 17, 18, 20-23, 27</u>
	No: Claims	<u>1, 15, 16, 19, 24-26</u>
Inventive step (IS)	Yes: Claims	<u>2, 8-14, 17, 18, 20-23, 27</u>
	No: Claims	<u>1, 3-7, 15, 16, 19, 24-26</u>
Industrial applicability (IA)	Yes: Claims	<u>1-27</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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 V

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

- 1 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.
- 2 Patentability, in particular novelty and inventive step, of claims 19 and 20 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.
- 3 Novelty (Article 33(2) PCT)
 - 3.1 The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 1, 15, 16, 19, 24-26 is not new.
 - 3.2 Document D1 discloses a conjugate comprising paclitaxel linked to a fatty acid of formula A2 wherein p is 15 and R⁴ is H. The conjugate has an improved plasma stability compared to unconjugated paclitaxel (abstract; figures 2, 3). Paclitaxel is linked to the fatty acid through a covalent bond, which can be considered as a "linker". Paclitaxel is a natural product and is therefore a biomolecule. The subject-matter of claims 1, 15, 16, 19, 24 is therefore not novel.
 - 3.3 Document D2 discloses a compound of formula A2 wherein p is 10 (D2, page 626, paragraph 3; page 627, paragraph 6). The subject-matter of claim 25 is therefore not novel.
 - 3.4 Document D3 discloses a compound of formula A1 wherein n is 14, m is 10, R¹ and R² are H and R³ is COOH (D3, page 86, compound 2). The subject-matter of claims 25 and 26 is therefore not novel.
- 4 Inventive step (Article 33(3) PCT)
 - 4.1 Being not new, the subject-matter of claims 1, 15, 16, 19, 24-26 cannot be considered as involving an inventive step.
 - 4.2 Dependent claims 3-7 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step. It would be obvious to the skilled person to shorten the aliphatic chain of the dicarboxylic fatty acid used in D1, thereby

arriving at a conjugate according to claim 3. It would also be obvious to the skilled person to insert a linker according to claims 4-7 between paclitaxel and the dicarboxylic fatty acid in D1.

4.3 As far as claim 2 is concerned, the skilled person would not have been prompted to conjugate paclitaxel to a fatty acid having two aliphatic chains. Claim 2 therefore meets the requirements of the PCT in respect of novelty and inventive step.

4.4 Document D4 is regarded as being the prior art closest to the subject-matter of claims 8 and 14 and discloses conjugates of fatty acids to the N-terminus of octreotate.

The subject-matter of claims 8 and 14 therefore differs from this known D4 in that octreotate is conjugated to a fatty acid of formula A1, A2 or A3 and is therefore new (Article 33(2) PCT).

The problem to be solved by the present invention may be regarded as the provision of alternative fatty acid-peptide conjugates.

The solution to this problem proposed in claims 8 and 14 of the present application is considered as involving an inventive step (Article 33(3) PCT) because the skilled person would not have been prompted to conjugate octreotate to a further aliphatic chain or to a dicarboxylic fatty acid. Claims 8 and 14 therefore meet the requirements of the PCT in respect of novelty and inventive step.

4.5 As for claims 9-13, 17, 18, 20-23, 27, none of the prior art documents neither discloses nor suggests conjugates of GDF15 to a fatty acid of formula A1, A2 or A3 or the compounds depicted in claim 27. Claims 9-13, 17, 18, 20-23, 27 therefore meet the requirements of the PCT in respect of novelty and inventive step.

Re Item VI

Certain documents cited

Patent No	Publication date	Filing date	Priority date
WO2015/013168	29.01.2015	21.07.2014	23.06.2014
WO2015/013169	29.01.2015	21.07.2014	23.06.2014
WO2015/006728	15.01.2015	11.07.2014	23.06.2014

The examination has been carried out assuming that the priority of the application is valid. However, attention is drawn to the fact that the document which has been cited in the search report as "P" document may become relevant in the national/regional examination phase.

Re Item VIII

Certain observations on the international application

- 1 The term "linker" in claim 1 renders its scope unclear (Article 6 PCT), since it is not known to the skilled reader which structures are intended to be encompassed by this term. Terms like "linker" include mere covalent bonds
- 2 Claim 25 is directed to compounds of formula A2 which are not clearly defined (Article 6 PCT) because the definition of "p" is missing. It was assumed that p is an integer between 6 and 30.