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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2015/070504	08.09.2015	08.09.2014

International Patent Classification (IPC) or both national classification and IPC
INV. A61K38/05 C07K5/06 A61P3/04

Applicant
LANDSTEINER GENMED, S.L.

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 notifed 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:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Winger, Rudolf 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 43*bis*.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 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).

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. 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.

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

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-25
	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

1.1 According to Rule 13.1 PCT a group of inventions is unitary if the group is linked so as to form a single general inventive concept. The link is present if there is a technical relationship between the inventions involving one or more of the same or corresponding special technical features pursuant to Rule 13.2 PCT. This special technical feature should define the contribution of the inventions over the prior art, i.e. be the reason for which the single general concept is novel and inventive.

In the present case invention 1 is directed to uses of compounds of formula (I) while invention 2 relates to compounds of formula (II).

The special technical feature in the present case is a common structural feature which is the dipeptidyl ketoamide core structure.

However, documents US 5514694 and US 5610297 already disclose compounds having the same structural features, i.e. the dipeptidyl ketoamide core structure, especially the compounds of tables 3 and 4 and examples 1, 4 and 7-10, respectively.

Furthermore, document WO 00/16767 and WO 2005/056519 disclose also compounds having the same structural features, i.e. the dipeptidyl ketoamide core structure, especially the compounds of examples 1, 2, 5 and 14 and formula (I), respectively.

It is noted that the specific compounds of said documents are disclaimed in invention II, however, they still fall within formula (I).

Therefore, the technical features common to all inventions and thus the single general concept are already known. There is no special technical feature in the sense of Rule 13.2 PCT providing a link between all claimed inventions so as to form a single general inventive concept.

The application does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

1.2 Hence, the following separate inventions or groups of inventions are not so linked as to form a single general inventive concept:

claims: 1-13

A compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention obesity-related conditions selected from the group consisting of obesity, lipid storage disease and hyperlipemia as well as the non-therapeutic use to reduce fat accumulation in a subject which does not suffer from obesity.

claims: 14-25

A compound of formula (II), a process for its preparation and its use as a medicament.

Re Item V

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

2 Claim 11 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. Furthermore and with regard to claim 10 it may also be helpful to note that the EPO also no longer accepts "Swiss" type claims in applications having a filing or an earliest priority date after 29.01.2011. Only claims drafted in the general form "*compound/composition for use in*" a wholly therapeutic method can be accepted as being a medical indication claim. Furthermore any dependent claims defining such a medical indication should be drafted in the form "*compound/composition for use according to*" a previous claim (rather than e.g. "*The compound/composition of*" a previous claim).

3 Prior Art: Reference is made to the following documents cited in the International Search Report and the passages identified therein:

D1	US 5 514 694 A (POWERS JAMES C [US] ET AL) 7 May 1996 (1996-05-07)
D2	US 5 610 297 A (POWERS JAMES C [US]) 11 March 1997 (1997-03-11)
D3	WO 00/16767 A1 (CEPHALON INC [US]) 30 March 2000 (2000-03-30)

D4 WO 2005/056519 A1 (SENJU PHARMA CO [JP]; SHIRASAKI YOSHIHISA [JP]; MIYASHITA HIROYUKI [JP]) 23 June 2005 (2005-06-23)

D5 ALICE LEE-DUTRA ET AL: "Cathepsin S inhibitors: 2004 - 2010", EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 21, no. 3, 1 March 2011 (2011-03-01), pages 311-337, XP055100095, ISSN: 1354-3776, DOI: 10.1517/13543776.2011.553800

3.1 Documents D1 and D2 disclose dipeptidyl ketoamides of formula (I) and their in vivo uses auch as the treatment of ischemia, stroke, restenosis or Alzheimer's disease.

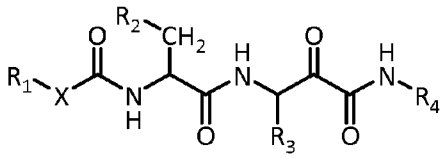
3.2 Documents D3 discloses dipeptidyl ketoamides of formula (I) and their in vivo uses such as the treatment of neurodegeneration, stroke or Alzheimer's.

3.3 Document D4 discloses dipeptidyl ketoamides of formula (I) and their in vivo uses such as the treatment of ischemic disease or Alzheimer's disease.

3.4 Document D5 discloses that Cat S inhibition may have applications as therapy against Alzheimer's disease, atherosclerosis and obesity while suitable inhibitors are alpha-ketoamides.

4 **Invention 1**

4.1 Claim 1 relates to a compound of formula (I):



(I)

.... for use in the treatment and/or prevention obesity-related conditions selected form the group consisting of obesity, lipid storage disease and hyperlipemia, while claim 10 and 11 relate to the corresponding uses and methods and claim 12 relates to the corresponding non-therapeutic use.

4.2 Document D5 which may be regarded as being the prior art closest to the subject-matter of claim 1 differs with respect to the ketoamides used.

4.3 It is noted that in the examples it has been shown that a variety of compounds of formula (I) inhibit adipogenesis.

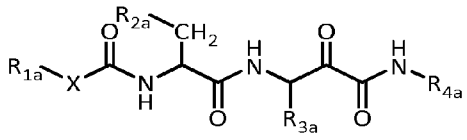
4.4 Thus, the problem to be solved by the present invention may therefore be regarded as to provide alternative ketoamides for the reduction of fat accumulation.

4.5 The solution proposed in claims 1, 10, 11 and 12 of the present application cannot be considered to involve an inventive step (Article 33(3) PCT) because the replacement by the ketoamides of documents D1-D4 seems to be within the standard practice of the skilled person and as such an obvious alternative.

4.6 The dependent claims do not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step.

5 **Invention 2**

5.1 Claim 14 relates to a compound of formula (II):



(II)

...., while claims 23-25 relate to the process for the preparation of a compound of formula (II), to the corresponding pharmaceutical composition and to its use as a medicament, respectively.

5.1.1 It is noted that claim 14 is delimited from documents D1-D4 only by means of a disclaimer. However, such a disclaimer does not render inventive the subject-matter of said claim as it is still obvious over said documents in that arbitrary alternatives are selected.

5.1.2 Furthermore it is noted that in the examples it has been shown that a variety of compounds of formula (II) with R2a being isopropyl and R3a being benzyl inhibit adipogenesis. Thus, it does not seem plausible that all the other compounds claimed would solve the problem posed.

5.1.3 Thus, the subject-matter of claims 14 and 23-25 of the present application cannot be considered to involve an inventive step (Article 33(3) PCT).

5.1.4 The dependent claims do not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step.

Re Item VIII

Certain observations on the international application

6 The application does not meet the requirements of Article 6 PCT because it is not clear whether in dependent claim 3 there are any limitations for R1 and in dependent claim 4 any limitation for X, respectively.